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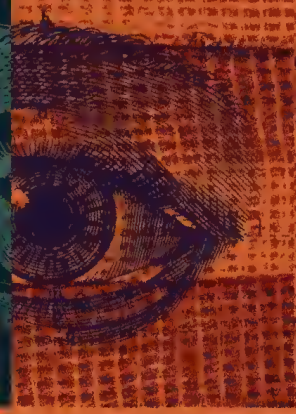
Medical Discoveries



Medical Breakthroughs and the People Who Developed Them

Bridget Travers and
Fran Locher Freiman, Editors

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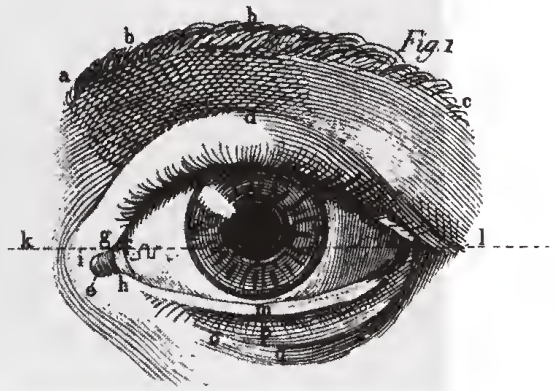

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Bridget Travers and Fran Locher Freiman, Editors

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Reader's Guide

Medical Discoveries: Medical Breakthroughs and the People Who Developed Them features 215 entries on medical and dental inventions and discoveries that have had a great impact on health throughout the world—from fluoride treatments to AIDS therapies—as well as the people responsible for them. Written in nontechnical language, *Medical Discoveries* explores medical practices such as acupuncture, significant developments in research such as chemotherapy, and instrumentation such as X-ray machines that have profoundly changed the way diseases are diagnosed and people are treated.

Each *Medical Discoveries* entry, whether on a well-known discovery or a lesser-known invention, identifies the person behind the breakthrough, explores the knowledge and technology that led to it, and explains how the advance changed the world in which we live.

Scope

Arranged alphabetically over three volumes, *Medical Discoveries*'s entries range from one-quarter to seven pages in length. Accompanying several of the entries are sidebar boxes discussing related topics and items of special interest to students, such as the discovery of DNA structure. Boldfaced terms in entry text direct the reader to related entries in the set. Cross-references at the end of an entry direct the reader to related breakthroughs and discoveries not specifically mentioned in that entry. More than 150 photographs enliven and help explain the text.

Each *Medical Discoveries* volume opens with a further readings page that guides readers to titles of similar interest, a timeline of medical and dental landmarks, and a glossary of important medical and dental terms found in the text. The volumes conclude with a comprehensive gen-

eral index, providing easy access to the people, theories, and discoveries and inventions mentioned throughout *Medical Discoveries.*

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Comments and Suggestions

We welcome your comments on this work as well as your suggestions for topics to be featured in future editions of *Medical Discoveries: Medical Breakthroughs and the People Who Developed Them.* Please write: Editors, *Medical Discoveries,* U·X·L, 835 Penobscot Bldg., Detroit, Michigan 48226-4094; call toll-free: 1-800-877-4253; or fax 1-313-877-6348.

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Timeline of Medical Events

4000 B.C.: Babylonians use opium in medical procedures.

3000 B.C.: First recorded cesarean surgeries are performed in Egypt.

762 B.C.: Wang Ping compiles an edition of the *Nei Ching*, a basic reference book on acupuncture.

700 B.C.: Etruscans construct false teeth from ivory and bone.

c. 600 B.C.: Skin graft surgery is successfully performed in India.

c. 400 B.C.: Hippocrates studies how disease is spread from person to person.

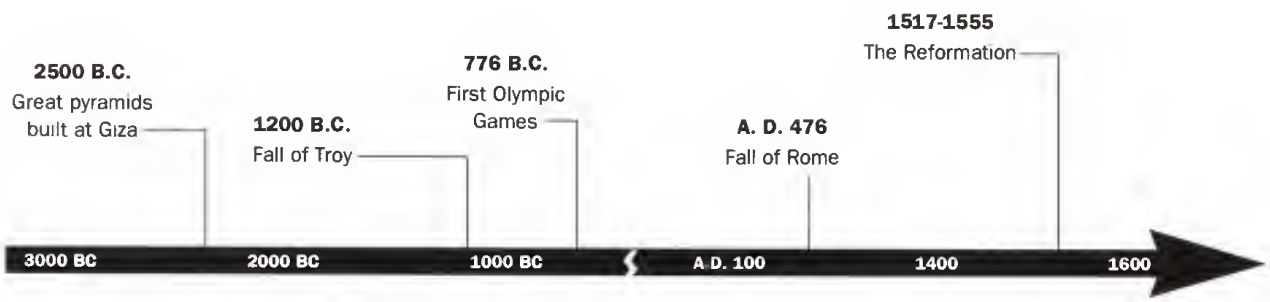
c. A.D. 160: Galen conducts extensive studies of animal anatomy.

1285: Salvino degli Armati invents eyeglasses.

1492: Pope Innocent VIII receives the first recorded blood transfusion.

1536: Surgeon Ambroise Paré designs the first artificial limbs.

1543: Anatomist Andreas Vesalius publishes his influential medical text about the human body called *De humani corporis fabrica*.



Early 1600s: Bristle-style toothbrush is introduced in Europe.

1616: Dr. William Harvey lectures about blood circulation.

1748: J. Daviel performs the first cataract operation.

1792: Dominique-Jean Larrey begins the first field ambulance service.

1796: Edward Jenner develops the smallpox vaccine.

1816: Rene Theophile Laennec invents the modern stethoscope.

1818: Humphry Davy discovers nitrous oxide, or "laughing gas."

1835: Theodor Schwann uncovers pepsin in gastric juice.

c. 1850s: Louis Pasteur develops the theory that germs cause disease by interfering with the body's biological processes.

1852: Antonius Mathijsen develops plaster of paris casts for setting fractures.

1853: Charles Pravaz invents the hypodermic syringe.

1865: Joseph Lister introduces antiseptic surgical procedures.

1866: Sir Thomas Clifford Allbutt invents the medical thermometer.

1866: Pasteurization is first used prevent wine spoilage.

1876: Siegfried von Basch invents the modern blood pressure measuring device.

1879: Listerine is introduced as a patent medicine.

1880: Gregor Mendel discovers hereditary factors in plants.

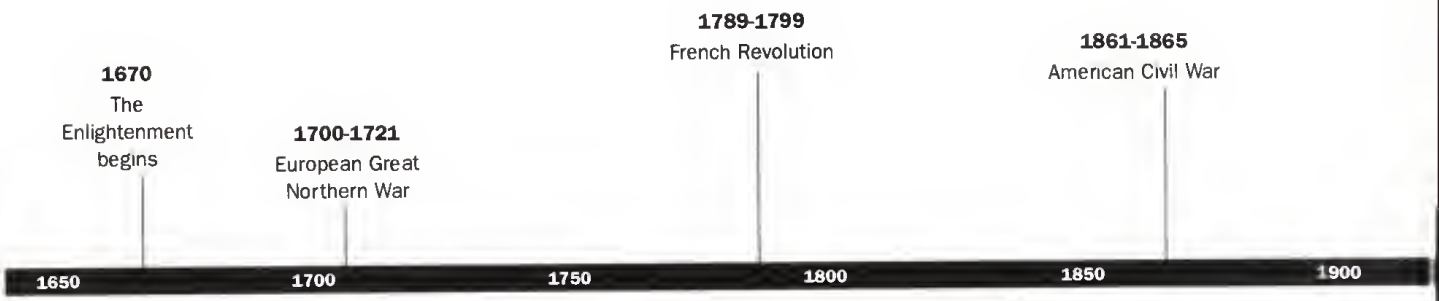
c. 1880: Elie Metchnikoff discovers the role white blood cells play in disease control.

1888: Eugene Kalt develops first contact lens.

1895: Wilhelm Roentgen discovers X-ray radiation.

1899: The Bayer Company begins producing aspirin.

1900: Karl Landsteiner discovers blood groups, or types.



1905: Ernest Starling and William Bayliss isolate secretin.

1906: Frederick Gowland Hopkins discovers vitamins.

1913: John Jacob Abel builds the first kidney dialysis machine.

1913: William Henry Bragg and his son, William Lawrence Bragg, construct the first X-ray spectroscope.

1920: Earl Dickson invents the Band-Aid.

1928: Ernst Ruska develops the electron microscope.

1931: Frederick S. McKay discovers that fluoride prevents tooth decay.

1937: Daniele Bovet and Anne-marie Staub synthesize antihistamine for allergy relief.

1938: Alexander Fleming, Howard Florey, and Ernst Chain discover penicillin.

1939: George Nicholas Papanicolau develops the pap test for detecting cervical cancer.

c. 1950: The first prenatal surgery is performed.

1952: Virginia Apgar develops a scoring system to help determine the health of newborn babies.

1953: Francis Crick and James Watson discover the structure of DNA.

1955: Radial keratotomy is first performed in Japan.

1955: Johnson & Johnson introduces Tylenol.

1957: Ian Donald tests ultrasound diagnostic instrument.

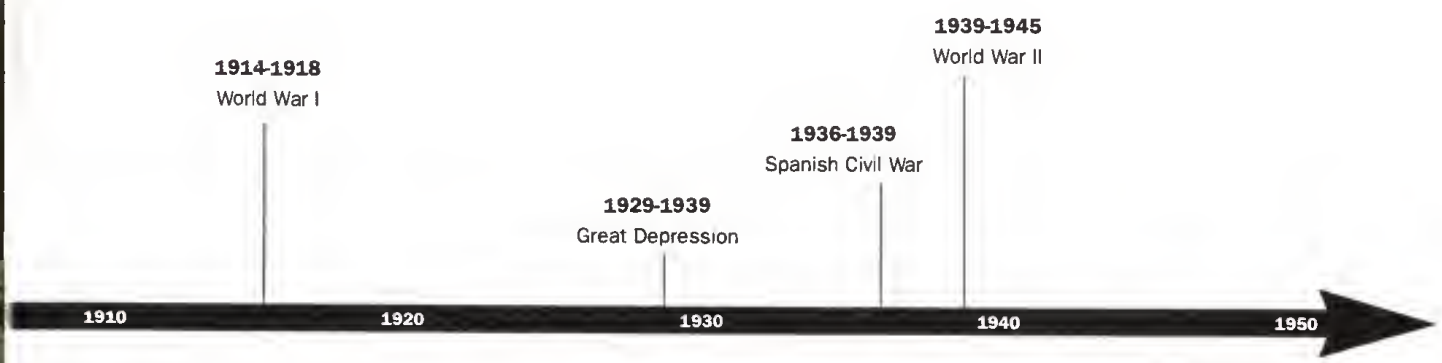
1960: Birth control pill is approved for general use.

1960: First pacemaker is implanted in a human to regulate heartbeat.

1964: Boots Laboratories begins selling ibuprofen under the brand name Brufen.

1967: Christiaan Barnard performs the first heart transplant.

c. 1967: Alan Cormack and Godfrey Hounsfield develop the computerized axial tomography (CAT) scanner.



1969: Denton Cooley implants first human artificial heart

c. 1970: Michael Phelps and Edward Hoffman develop the positron emission tomography (PET) scanner.

Early 1970s: Laser surgery techniques are perfected.

1973: Cochlear implants are used for the first time to improve hearing.

1976: The retinal scanner is developed.

1978: The first "test tube" baby is born as a result of in vitro fertilization.

c. 1981: Magnetic resonance imaging (MRI) testing is first used for diagnosing illness.

1984: Drug AZT is developed for the treatment of AIDs.

1985: Gerd Binnig, Christoph Gerber, and Calvin Quate invent the atomic force microscope.

1985: Alec Jeffreys develops genetic fingerprinting.

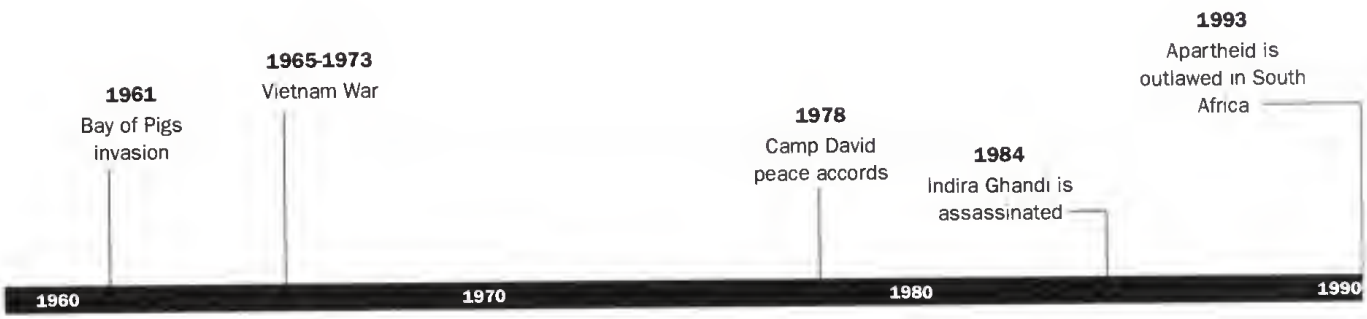
1986: Laparascopic techniques allow surgery to be performed with less trauma to the body.

1992: John Daugman introduces the iris scanner.

1992: Researchers announce a link between folic acid deficiency and spinal cord birth defects.

1996: Protease inhibitor drugs hailed as newest tool in AIDs treatment.

1996: RU 486 is approved by the FDA for use in the United States.



Words to Know

A

adhesive: a substance that causes one object to stick to another.

alkaloid: any of various organic compounds containing at least one nitrogen atom. Alkaloids occur mainly in many plants and some fungi. Many alkaloids, such as nicotine, cocaine, and morphine, are known for both their addictive and medicinal qualities.

amino acids: organic compounds of nitrogen and hydrogen that combine with other elements to produce proteins.

analgesic: a substance that reduces or eliminates pain.

angina: severe chest pain associated with narrowing of arteries and reduction of blood flow to the heart.

antigen: a substance that, when introduced into the body, stimulates the production of an antibody. Antigens include toxins, bacteria, foreign blood cells, and the cells of transplanted organs.

antioxidant: a substance that prevents fatty acids from combining with oxygen.

antiseptic: a substance that stops the growth of organisms that cause infection.

aspirate: to remove liquids or gases using a suction device.

B

benign: harmless; without bad intent.

blood serum: the part of the blood that does not contain blood cells. Also called plasma.

C

cardiovascular: having to do with the heart and blood circulation systems.

carotene: an orange-red substance that is changed to vitamin A in the liver.

catalyst: a substance that speeds up chemical reactions without undergoing change itself.

cauterization: use of heat to seal wounded blood vessels and prevent uncontrolled bleeding.

chlorofluorocarbons (CFCs): very stable molecules made up of chlorine, fluorine and carbon, commonly used in aerosol products and for refrigeration.

cholesterol: an organic substance found in animal tissues and various foods. Cholesterol is normally synthesized by the liver and is important as a part of cell membranes. The cholesterol level in the bloodstream can influence certain conditions, such as the development of atherosclerotic plaque and coronary artery disease.

chromosome: a threadlike strand of DNA and associated proteins in the nucleus of animal and plant cells that carries the genes that transmit hereditary information.

coenzyme: any of a group of organic compounds that usually contain a vitamin or mineral. These compounds combine with proteins to form enzymes.

collagen: a protein that makes up connective tissues such as ligaments and tendons.

congenital: something present in the body from the time of birth.

contraception: birth control.

contrast agent: dye injected into the human blood stream to detect blockages in blood flow.

cornea: the transparent covering of the eye.

coronary: of or relating to the heart and the arteries and veins which are attached to it.

D

diffraction: a change in the direction of a group of waves, such as light waves, when they strike an object or pass through a small opening.

diffusion: the continual movement of molecules in air or water.

distillation: the process of separating alcohol from the grains and fruits it was fermented from and condensing the separated alcohol into pure liquid.

dressing: materials used to cover wounds.

E

embryo: an unborn animal in the initial stages of development; an unborn human, from implantation of the fertilized egg in the uterus through the eighth week of the pregnancy.

emulsify: the suspension of one liquid inside another in which the liquids do not mix together, such as oil in water.

endocrine glands: any of a group of glands that produce hormones.

enzyme: any of numerous proteins produced by living organisms that function as catalysts, or starters, for biochemical reactions.

F

fermentation: the process of transforming sugar into alcohol.

fetus: an unborn animal in the mid-to-later stages of development; in an unborn human, the fourth to ninth month of the mother's pregnancy.

G

glucose: a monosaccharide sugar occurring widely in most plant and animal tissue. Glucose is the main circulating sugar in the blood and the major energy source of the body.

glycogen: a polysaccharide that helps with carbohydrate storage in animals. Glycogen occurs primarily in the liver and in muscle tissue.

H

hemoglobin: the iron-containing protein in the blood's red cells which carries oxygen to the cells of the body.

hemorrhage: uncontrolled bleeding.

heredity: the physical characteristics passed by the genes from one organism to another.

hypothalamus: the part of the brain that lies below the thalamus, or lower portion. Its functions are to regulate bodily temperature, certain metabolic processes, and other involuntary body activities.

I

immunosuppressant: a substance that prevents the immune system from attacking transplanted organs.

inebriation: state of the body after consuming too much alcohol.

inert: chemically inactive; a material unable to react with other chemicals.

infertility: the inability to have children.

inflammation: a localized protective reaction of tissue to irritation, injury, or infection, characterized by pain, redness, swelling, and sometimes, loss of function.

invasive: involving entry into the living body.

ion: an atom or a group of atoms that has an electric charge by gaining or losing one or more electrons.

isotope: one of two or more atoms of the same chemical element but with different masses.

L

lacerations: cuts or openings in the skin caused by injury.

leukocyte: any of the white blood cells that fight disease in the body.

ligament: a band of tough, elastic tissue that binds bones together at a joint.

ligature: the tying off of blood vessels in order to prevent uncontrolled bleeding.

lipids: a group of organic compounds, including fats, oils, waxes, sterols, and triglycerides, that are insoluble in water but soluble in common organic solvents, are oily to the touch and, together with carbohydrates and proteins, make up the principal structural material of living cells.

lymphocyte: white blood cells produced by the lymphatic tissues of the body. Lymphocytes function in the development of immunity.

M

malignant: acting with the purpose of harming.

malocclusion: a term for teeth that are crooked or misaligned.

midwife: a medically trained person, though not a doctor, who specializes in assisting with childbirth.

miscarriage: a spontaneous (unplanned) abortion of an embryo or fetus.

N

neoplasm: any of a group of cells that grow more rapidly than normal.

neurology: the study of the nervous system.

neuron: any of the impulse-conducting cells that make up the brain, spinal column, and nerves. Also called nerve cells.

nucleic acids: group of acid substances found in the nucleus of all living cells.

O

obstetrics: the medical study of childbirth.

opiate: chemicals derived from opium, a product of the poppy plant. When injected, opium gives a feeling of relaxation and happiness and relieves feelings of pain. Opiates include heroin, morphine, and methadone.

osmosis: the movement of water across a membrane (barrier) when there is a different concentration of molecules on one side of the membrane than on the other.

ovum: the egg of the human female which originates in the ovaries.

oxidant: a chemical compound that combines with other compounds to produce oxides and water.

ozone: a form of oxygen molecule with three atoms of oxygen.

P

pathology: the study of diseases.

peptide: any of various natural or synthetic compounds containing two or more amino acids linked together.

pharmaceutical: having to do with the development and distribution of drugs for medical uses.

placenta: an organ which lines the uterus and holds a fetus and its fluids during the mother's pregnancy; also contains the blood supply through which nutrition and oxygen are passed to the fetus through the umbilical cord.

plasma: that part of the blood which does not contain the blood cells. Also called blood serum.

prognosis: a prediction of the probable course and outcome of a disease.

prosthesis: an artificial limb.

puberty: the stage of adolescence when a person undergoes bodily changes, such as the onset of menstruation and the growth of facial hair.

R

retina: a light-sensitive membrane lining the inner eyeball and connected by the optic nerve to the brain.

retrovirus: a virus that invades a healthy cell and copies its DNA (genetic information) to that cell.

S

soluble: capable of being dissolved.

sputum: mucus from the lungs.

sterility: inability to have children

steroid: any of a group of fat-soluble organic compounds, including the sterols and bile acids, and adrenal and sex hormones.

sublime: to pass directly from a solid to a vapor, skipping the liquid state.

sutures: surgical stitches to hold the edges of a wound together.

synthetic: substances produced by human attempts to blend or combine materials that do not naturally occur together.

systemic: acting throughout an entire system. Systemic medications affect the whole body, not just a small part.

T

tachycardia: a fast, irregular heartbeat.

T-cell: white blood cells that attack disease-causing organisms or other foreign bodies, such as transplanted organs, in the body.

therapeutic: something used for treatment of illness.

thrombolysis: process of dissolving blood clots.

toxin: an invading organism that will cause disease and damage the body.

toxoid: a disease-causing organism that is chemically treated to end its ability to cause disease. Treated toxoids help generate immunity.

tubal ligation: the tying of ovarian tubes in the female to prevent the release of ova (eggs) and provide permanent birth control.

U

ultrasound: frequencies above the range of human hearing; in medicine, the use of ultrasonic waves to create pictures of internal body structures and organs.

V

vas deferens: the tubes that connect the male testicles to the penis.

vasectomy: the cutting and tying of testicular tubes in the male to prevent sperm from causing a pregnancy.

ventricular fibrillation: irregular contractions of the heart.

volatility: ability of a liquid to change to a gas at room temperature.

Z

zygote: a fertilized ovum or egg.

Davy, Humphry

Humphry Davy (1778-1829) grew up poor, helping his mother pay off debts left by his father, a woodcarver who had lost his earnings in speculative investments. Davy's education was not outstanding, since he could not afford to go to very good schools. Still, Davy managed to absorb lots of classic literature and science. In later life, he said he was happy he did not have to study too hard in school so that he had more time to think on his own.

Without money for further education, seventeen-year-old Davy began to serve as an apprentice to a pharmacist/surgeon. During this time, Davy took it upon himself to learn more about whatever interested him, including geography, languages, philosophy, and science. When he was nineteen years old, Davy read a book on chemistry by famous French chemist Antoine-Laurent Lavoisier (1743-1794) that convinced him to concentrate on that subject. For the rest of his life, Davy's career was marked by brilliant, if sometimes hasty, scientific explorations in chemistry and electrochemistry.

Conducts Research on Himself

One of Davy's scientific trademarks was his willingness, even eagerness, to use himself as a guinea pig. In the process of conducting experiments on the therapeutic (healing) properties of various gases, he breathed four quarts of pure hydrogen and nearly suffocated. In one instance, Davy's fondness for risk paid off. While studying **nitrous oxide** gas, he discovered that it made him feel dizzy and euphoric (happy and silly). When he encouraged his friends to inhale the gas with him, he found that their inhi-

bitions were lowered and their feelings of happiness or sadness intensified. Davy's poet friend Robert Southey (1774-1843) referred to his experience as being "turned on," and nitrous oxide became known as laughing gas. Beyond Davy's circle, nitrous oxide parties became a fad among wealthy people.

Davy recognized, however, that the gas could also be used to dull physical pain during minor surgery. Although the medical profession ignored this discovery for nearly 50 years, nitrous oxide eventually became the first chemical **anesthetic.** In an 1844 experiment, a dentist had one of his teeth extracted successfully while under the influence of nitrous oxide, having first taken the precaution of writing his will). Some dentists still use the gas today for nervous patients, especially children.

Other Accomplishments

Davy's research credits beyond nitrous oxide are many. His style in the laboratory was to work quickly and intensely, pursuing one new idea after another. He aimed at originality and creativity, rather than tediously repeating tests and confirming results. Some of his later discoveries include several chemical elements, **arc lighting,** and the invention of a safer miner's lamp.

Davy was known for his charm and good looks, as well. While in his early thirties, after being knighted in 1812, Davy married a wealthy Scottish widow and began to travel extensively and enjoy his fame. In addition to his knighthood, Davy was made a baronet (a British hereditary title of honor) in 1818 for his service to the mining industry and was elected president of the prestigious Royal Society in 1820. In his conflicts with other scientists, however, Davy made some enemies who thought he was arrogant.

Ill health began to plague Davy while he was still in his thirties. The same curiosity that drove him to discover and invent with such success had also taken its toll on his body. By sniffing and tasting unknown chemicals, he had poisoned his system; his eyes had also been damaged in a laboratory explosion. Although Davy continued to pursue scientific interests, he suffered a stroke at age forty-nine and died just two years later.

DDT

DDT (dichloro-diphenyl-trichloroethane) is perhaps the most recognized of all insecticides because it's use helped reveal the many hazards associated with synthetic (man-made) pesticides. This colorless, odorless, insoluble toxic pesticide contains up to fourteen chemical compounds. It is

known for its ability to eradicate (destroy) pesky insects such as flies, lice, and mosquitoes, as well as agricultural pests. Although first synthesized in 1874 by German chemist Othmar Zeidler, DDT was not used as an insecticide until 1939. It was then that Swiss scientist Paul Hermann Müller (1899-1965) discovered its insect-killing properties.

DDT is very durable. In some applications it is effective for 12 years. Water cannot wash it away and it resists breakdown by light and air. Its strength and persistence have resulted in DDT's transfer to "non-target" living organisms. Once in an ecosystem (an inter-related community of animals, plants, and bacteria), it can pass on from crops to birds and from water to fish, eventually affecting the whole food chain.

DDT Exposure

When ingested by humans, DDT is stored in body fats and can be passed on to nursing babies. Low levels of DDT in humans are harmless but large concentrations can cause severe health problems such as liver cancer. When applied to an insect, DDT is easily absorbed through the body surface. After attacking the nervous system, DDT causes paralysis. Some insects have a resistance to DDT, thereby making the insecticide ineffective. These resistant insects are able to reproduce and pass this trait on to their offspring.

Many problems arise when larger animals are exposed to DDT or eat smaller animals that have ingested (eaten) the toxin (poison). For example, while DDT is more toxic to fish than birds, it still causes widespread bird deaths. With high levels of exposure, DDT causes convulsions and paralyzes the birds' nerve centers. In smaller concentrations, it can weaken their egg shells and can cause sharp declines in the species' reproductive rate. DDT ingestion by peregrine falcons is thought to have caused their almost complete extinction in most regions of the United States.

DDT ingestion by peregrine falcons is thought to have caused their almost complete extinction in most regions of the United States.

The Benefits of DDT

The benefits of DDT were demonstrated in the 1940s when it was used in World War II (1939-1945) to clear out mosquito-infested areas prior to invasion. Even after the war, the use of DDT in the United States almost completely wiped out malaria (an infectious disease characterized by severe chills and fever) and yellow fever. In tropical areas, the use of DDT has helped save millions of lives that would otherwise have been lost to disease. DDT was also routinely applied as a crop dust or water spray on orchards, gardens, fields, and forests. At one point it was registered for use on 334 agricultural crops.

As part of a 1945 experiment, two researchers drain an artificial pond to see if fish were harmed by exposure to a DDT.

In 1962 Rachel Carson's (1907-1964) landmark book, *Silent Spring*, exposed the dangers of unregulated pesticide use. Spurred by public pressure, state and federal governments turned their attention to the regulation of pesticides. In 1972, the United States Environmental Protection Agency (EPA) banned the use of DDT. Today, DDT is restricted in the United States, Europe, and Japan. However, many other countries still use DDT widely for malaria control, delousing, and the eradication of other disease-spreading insects.

Defibrillator and cardioverter

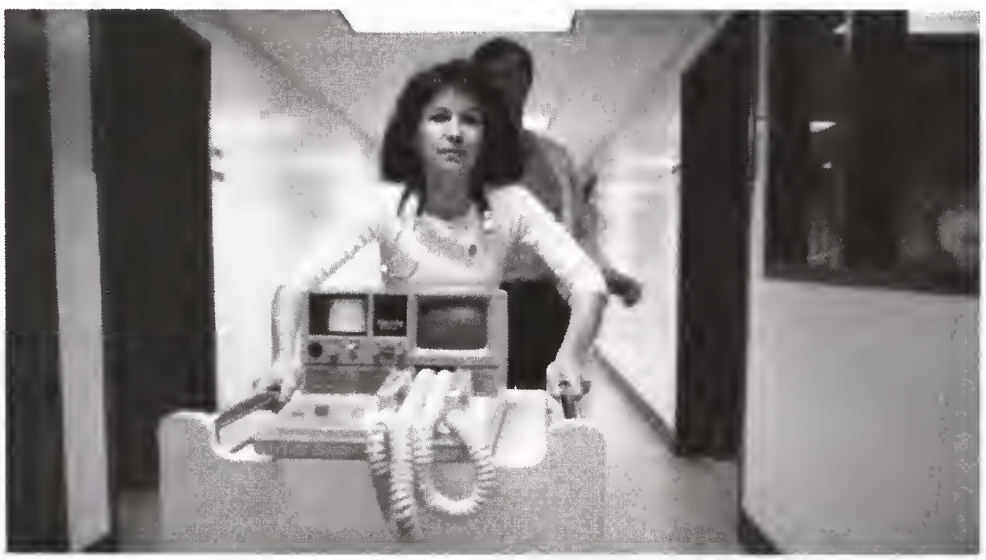
Ventricular fibrillation occurs when the individual muscles of the heart contract in a random, uncoordinated way. The heart appears to shiver, and

blood circulation ceases. Ventricular fibrillation is fatal unless normal heart contraction is quickly restored.

Early Defibrillators

As early as 1899 Prevost and Batelli were able to stop ventricular fibrillation in a dog. They did this by applying an electric shock to the animal's exposed heart. Beck successfully used this technique on a human patient in 1947. In 1957 William B. Kouwenhoven, an American electrical engineer at Johns Hopkins University in Baltimore, Maryland, developed a closed-chest defibrillator. The unit was first tested on a dog. It sent electrical shocks to the heart through electrodes placed on the animal's chest. American cardiologist Paul Zoll applied this alternating current defibrillator to human patients in 1961. The direct current defibrillator introduced by Lown and Neuman in 1962 provided greater reliability and safety.

Defibrillators greatly improve the ability of patients to survive when their heart starts to fibrillate (rapidly contract). Heart surgery, invasive cardiac diagnostic and treatment techniques, and heart attacks all may trigger fibrillation. Since the 1970s, most hospital emergency rooms have been equipped with electric defibrillators. Portable devices are becoming standard equipment for **ambulances.** Automatic defibrillators have been developed that detect abnormal heartbeats and deliver the appropriate electrical shocks. Unlike standard defibrillators, these devices can be used by operators with much less training than paramedics. They can be used by on-site personnel such as firefighters before paramedics arrive.



Defibrillators greatly improve the ability of patients to survive when their heart starts to fibrillate, or rapidly contract.

Implantable Devices

An implantable device to stop heart arrhythmias was invented by Mieczyslaw Mirowski at Johns Hopkins. Mirowski's automatic implantable cardioverter defibrillator (AICD) was approved for use by the Food and Drug Administration (FDA) in 1985. It senses two kinds of abnormal heart rhythms and automatically sends an electric shock to the heart to correct the disturbance. As a defibrillator, the device jolts the heart out of ventricular fibrillation. As a cardioverter, it shocks the heart out of an abnormally fast heartbeat. The AICD requires more power than the standard cardiac **pacemaker** (an electronic mechanism inserted into the heart that regulates heartbeat). Its battery pack is separately implanted in the patient's abdomen (the part of the body between the diaphragm and the pelvis). **Lithium** batteries can deliver 100 to 150 shocks during their three-year lifetime.

The AICD is a potential lifesaver for the 700,000 people in the United States who survive heart attacks each year. These people are at risk for potentially fatal arrhythmias. The AICD is also routinely used for patients whose arrhythmias cannot be treated with medication or surgery.

Modern dental drills are turbine-powered and rotate at speeds of 300,000 to 400,000 revolutions per minute.

Dental drill

When a tooth develops a cavity, the decayed tissue must be removed. The earliest devices for doing this were picks and enamel scissors. Later, two-edged cutting instruments were designed that were twirled in both directions between the fingers. The father of modern dentistry, Frenchman Pierre Fauchard (1678-1761), described an improved drill in 1728. Its rotary (turning around a central point) movement was powered by catgut twisted around a cylinder, or by jewelers' bowstrings. A hand-cranked dental drill bit was patented by John Lewis in 1838. George Washington's dentist, John Greenwood (1760-1819), invented the first known "dental foot engine" in 1790. Greenwood adapted his mother's foot-treadle (pedal) spinning wheel to rotate a drill. Greenwood's dentist son continued to use the drill, but the idea went no further.

Early Drill Designs

Scottish inventor James Nasmyth used a coiled wire spring to drive a drill in 1829. Charles Merry of St. Louis, Missouri, adapted Nasmyth's drill by adding a flexible cable to it in 1858. The first motor-driven drill appeared in 1864, the design of Englishman George F. Harrington. This "motor drill" was a hand-held device powered by the spring action of a clock movement. In 1868 American George F. Green introduced a pneumatic (air-driven) drill powered by a pedal bellows. Fellow American James B. Morrison patented a pedal bur drill in 1871. A further improvement of the Nasmyth-Merry design, the bur drill featured a flexible arm with a handpiece to hold the drill, a foot treadle, and pulleys. Each of these developments increased the speed at which the drill operated.

In 1874, six years after he made his original contribution to drills, Green added electricity to the dental drill. Green's drill was powered by electromagnetic motors and worked well, but it was also heavy and expensive. Plug-in electric drills became available in 1908. By that time, most dental offices had electricity.

The Modern Dental Drill

Once efficient, mechanically-driven drills became widely available, teeth could be properly and accurately prepared for well-fitting **crowns** (an artificial substitute for the part of the tooth projecting beyond the gum line) and **fillings.** American teeth blossomed with the gold of inlays (a filling for a tooth made from a mold) and crowns. Modern dental drills are turbine-powered and rotate at speeds of 300,000 to 400,000 revolutions per minute. Drills generate a large amount of heat but are less irritating to the patient because the cutting action is smoother.

[*See also* **Dental fillings, crown, and bridge**]

Dental fillings, crowns, and bridges

Cavities (areas of decay) in teeth have been filled since earliest times with a variety of materials, including stone chips, turpentine resin (an organic plant substance), gum, and metals. Giovanni d'Arcoli recommended gold-leaf (gold beaten into very thin sheets) fillings in 1484. The renowned French physician **Ambroise Paré** (1510-1590) used lead or cork to fill teeth. In France of the 1700s, Pierre Fauchard (1678-1761; often referred to as "the father of modern dentistry") favored tin foil or lead cylinders.

Philip Pfaff (1715-1767), dentist to Frederick the Great of Prussia (1712-1786), used gold foil to cap teeth.

Gold leaf as a filling became popular in the United States in the early nineteenth century. Marcus Bull of Hartford, Connecticut, began producing beaten gold for dental use in 1812. In 1853 sponge gold was introduced in the United States and England to replace gold leaf. This was followed by the cohesive, or adhesive, gold introduced by American dentist Robert A. Arthur in 1855.

Amalgam Experimentation

The invention of the power-driven **dental drill** led to increased demand for fillings and for inexpensive filling material. Auguste Taveau of France developed the first dental amalgam (blend) in 1826. The amalgam was a solution of silver in mercury. When the French Crawcour brothers emigrated to the United States in 1833, they introduced Taveau's amalgam. Because of the amalgam's poor quality, many dentists refused to use it. Numerous experiments were carried out from the 1860s through the 1890s to develop improved amalgam filling materials. Chicago, Illinois, dentist G. V. Black (1836-1915) finally standardized both cavity preparation and amalgam manufacture in 1895.

Dental Cement

After truly effective dental cement was developed, baked porcelain (a hard, white ceramic) inlays came into use for filling large cavities. These were first described by B. Wood in 1862. In 1897 an Iowa dentist, B. F.

A dentist removes decay from a tooth.

Philbrook, described his method of casting metallic fillings. Philbrook used a wax impression that perfectly matched the shape of the cavity. Dr. William H. Taggart of Chicago described a similar method for casting gold inlays in 1907. This technique made possible the modern era of accurate filling and inlay fitting.

Crowns and Bridges

Crowns are used to replace and cover missing portions of teeth. Bridges are mountings for artificial teeth attached at either end to natural teeth. Both of these devices were made of gold and used by the Etruscans (people living in the ancient country of Etruria, an area of western Italy) 2,500 years ago. Crowns and bridges fell out of use during the Middle Ages and were only gradually rediscovered.

The gold shell crown was described by Pierre Mouton of France in 1746. It was not until 1873 that the gold shell crown was patented. The Logan crown, patented in 1885, used porcelain fused to a platinum post. It replaced the unsatisfactory wooden posts previously used. In 1907 the detached-post crown was introduced, which was more easily adjustable.

Bridge work developed as crowns did. Dentists would add extra facing to a crown to hold a replacement for an adjacent missing tooth. The major advance came with the detachable facings patented by Dr. Walter Mason of New Jersey in 1890 and the improved interchangeable facings introduced by the American dentist Thomas Steele in 1904. The common problem of broken facings was now easy to fix and permanent bridge installation became both possible and successful.

[*See also* **Adhesives and adhesive tape**]

Deoxyribonuclease

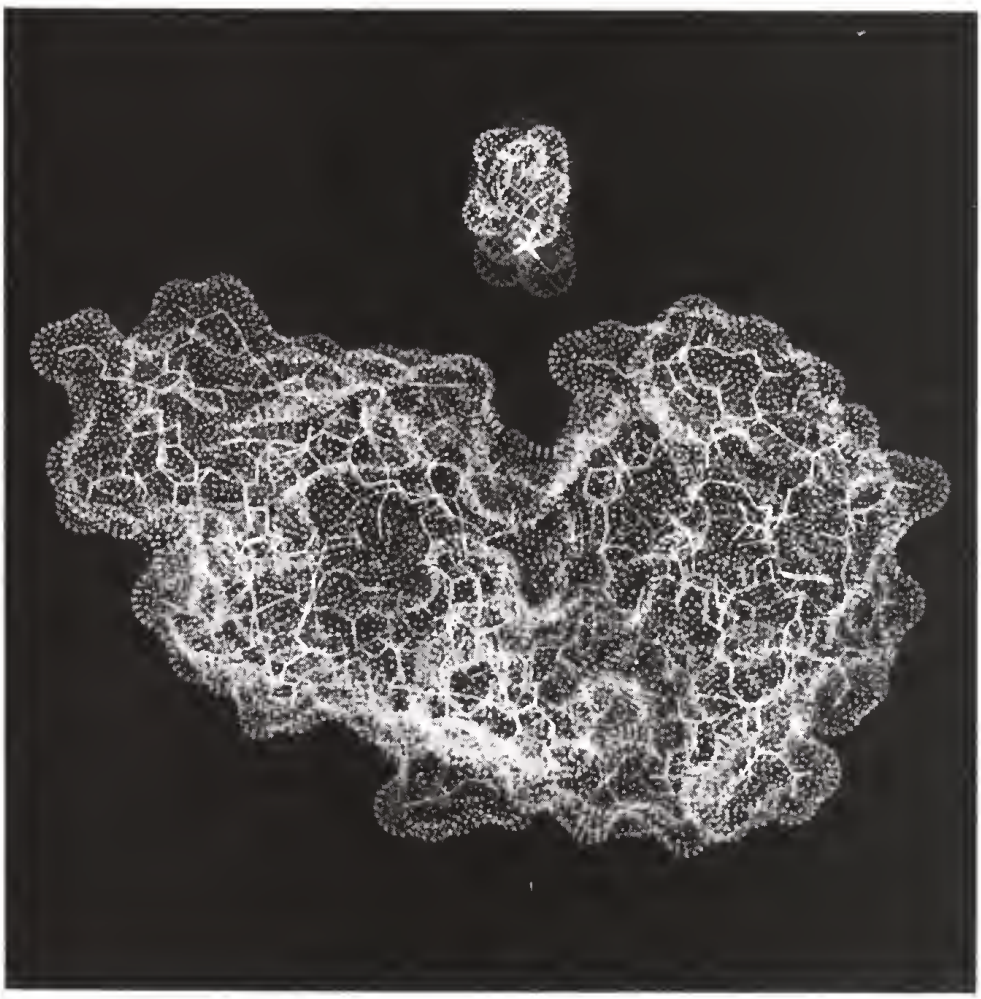
Deoxyribonuclease (pronounced "dee-oxy-rybo-noo-clee-ase"), or recombinant human deoxyribonuclease 1 (rhDNase or DNase), is an experimental drug used to treat cystic fibrosis (CF), an inherited lung disease. People with CF experience chronic (constant) and increasingly worse symptoms throughout their lives. CF patients often die in their late twenties. CF treatment has usually meant **antibiotics** and chest therapy (a physical pounding on the chest to loosen accumulated fluids).

DNase

Scientists discovered that the mucus (slimy secretion) of CF patients is full of DNA, which spills out of white blood cells as they die. DNase is an enzyme (a protein-like substance) that cuts the DNA present in the mucus. At first DNase was made from cows, but many patients had allergic reactions to it. Then a company separated the gene for human deoxyribonuclease, which chops up the protein but does not cause allergic reactions.

DNase is delivered to the patient in **aerosol** form, and it improves lung function by breaking up the thick mucus in the lungs. The patient is then able to clear the lungs by coughing. Considered among the ten most important advances of 1993—the year the drug was approved by the Food and Drug Administration (FDA)—it is also being considered for the treatment of chronic bronchitis.

[*See also* **Antihistamine; Enzyme; Gene; Gene therapy**]



Deoxyribonuclease.

Cystic Fibrosis

An inherited (genetic) disease that affects about 1 out of every 2,000 Caucasians of European descent, cystic fibrosis (CF) is the leading fatal genetic disease in the United States. CF occurs less frequently in African Americans and very rarely in Asians and Native Americans.

The disease causes a thick mucus to accumulate in the lungs, pancreas, and intestine. If the mucus blocks the lungs, the patient can die. Pneumonia, caused by bacterial infections, is a common problem for CF sufferers. People with CF suffer with abdominal (stomach) cramps, malnutrition, growth retardation, and coughing.

Other serious complications common in people with cystic fibrosis include respiratory (breathing) failure, diabetes, enlarged heart, liver cirrhosis (a disease in which liver cells are destroyed), intestinal blockage (bowel obstruction), pancreatic dysfunction (blocked ducts of the pancreas, preventing digestive **enzymes** from leaving the pancreas), sterility (inability to have children), and sodium (salt) deficiency. The increased saltiness of sweat is a highly useful test to diagnose CF, since predicting when any of these symptoms will appear or how severe they will be is a difficult task. Cystic fibrosis used to be fatal to nearly all children who developed it, but now more than 50 percent of CF patients live longer than 20 years.

Antihistamines and decongestants aid breathing by helping to open air passages. Antibiotics treat the pneumonia that often results from repeated lung infections. Physical therapy and surgery play roles in managing CF. Cough suppressants are avoided since coughing helps to loosen the mucus in the trachea and lungs. Newer treatments, such as DNase and **gene therapy,** have given mixed results.

Dialysis machine

Dialysis is the process of removing waste products from the blood. This removal is normally done by the kidneys, but if they are impaired (damaged), then a dialysis machine (also called an **artificial kidney**) can perform a similar function.

Early Dialysis Experiments

The first experiments with dialysis were performed using a dog in

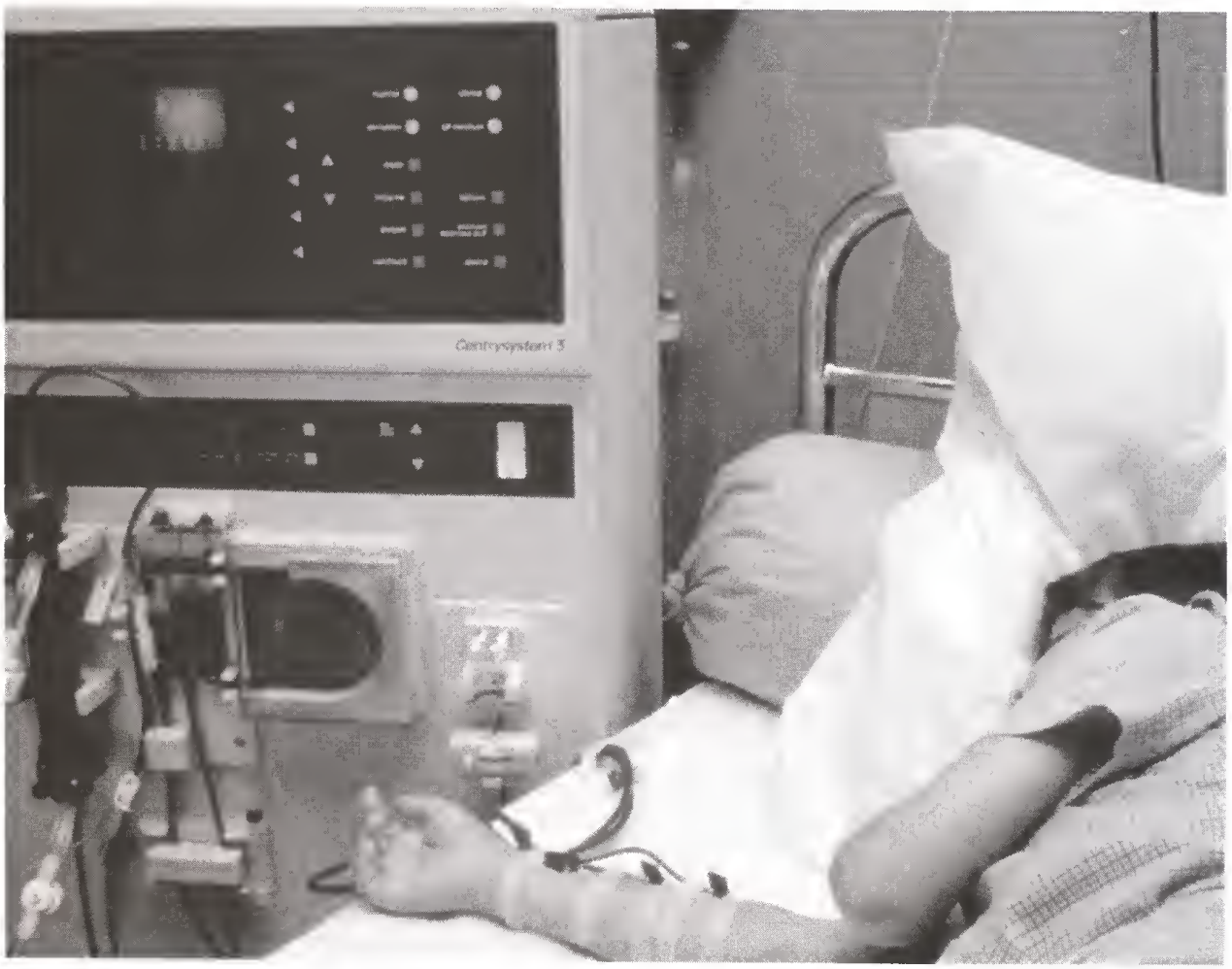
Dialysis machine

1913. John J. Abel, L. G. Rowntree, and B. B. Turner built a machine that pumped blood through a special membranous (thin, soft, and pliable) tube submerged in a liquid called dialysate. This tube had microscopic holes in it that let the waste products in the dog's blood seep through it and into the dialysate. One of the main problems that the experimenters had was that the dog's blood kept clotting. Until heparin, an anti-clotting medicine, was discovered, not many advances in dialysis were made.

Heparin was discovered by W. H. Howell in 1922. A transparent material called cellophane (used to separate waste products in the blood from the beneficial substances in it) was also invented. In 1945, William J. Kolff of Holland built the first dialysis machine that could be used by humans. Modifications by J. Merrell, K. Walter, and others in 1947 produced a smaller, more effective machine.

Biological Concepts

Dialysis involves four biological concepts: kidney filtration, semi-



A young patient receives dialysis treatment.

permeable membranes, diffusion, and osmosis. Humans have two kidneys through which blood is constantly being pumped. Special cells called glomeruli are responsible for removing waste products from the blood and at the same time balancing the amount of water in the body. There are also different kinds of particles (molecules) in the body that the kidney can separate, keeping the beneficial ones and excreting (getting rid of) the harmful ones.

The average human weighs about 70 kilograms (155 pounds), of which about 60 percent is water. This means there are about 40 liters (42 quarts) of body fluid. The body is made up of many cells. These cells and the surrounding tissue are responsible for storing the body fluids. There are two main compartments in which this fluid is stored. One is inside the cell and the other is outside the cell.

These two compartments are separated by a wall called the cell membrane. The cell membrane is a wall composed of three main building materials: fats, carbohydrates, and proteins. It is built this way so that only certain molecules can pass through it. This type of membrane is called a semipermeable membrane. Certain processes and conditions regulate the pressure and the flow of molecules through cell membranes, including permeability (some molecules can pass through but others cannot), concentration (there are different amounts of molecules on either side of the membrane), electrical potential (each molecule has an electric charge), and pressure (there can be different pressures on either side of the membrane).

Diffusion is the continual movement of molecules in air or water. Diffusion takes place when there is a greater concentration of molecules in one space relative to another. A simple experiment to demonstrate diffusion can be performed with perfume. If the perfume is placed in a shallow dish in the middle of a room, eventually it can be smelled everywhere in the room. That is because the molecules of perfume have diffused from an area of greater concentration (the dish of perfume) to an area of lesser concentration (the room). If a filter is placed over the dish of perfume, the smell might be a little bit different or weaker. This filter is similar to a membrane that allows only certain molecules to diffuse across it.

The movement of water (a solvent) across a membrane where there is a different concentration on either side is called osmosis. This means that in a container divided by a semipermeable membrane, with water on one side and a solution (water and other molecules) on the other, the water will flow through the membrane to the solution. The flow of water can be prevented by applying pressure to the solution side. The amount of pressure needed to stop osmosis is called osmotic pressure. If pressure is not applied

Dialysis machine

and osmosis is allowed to proceed, then osmosis stops when the water pressure (hydrostatic pressure) is equal to the osmotic pressure.

Hemodialysis

There are two different kinds of dialysis used in medicine: hemodialysis and peritoneal dialysis. The methods for performing dialysis may be different, but the goal of the treatment is the same, that is, to remove waste products. These wastes are composed mainly of nitrogen in the form of urea, uric acid, and creatinine.

Hemodialysis is diffusion across a semipermeable membrane (one that allows only certain molecules to pass through it). The semipermeable membrane is used to remove the wastes from the blood and at the same time correct the level of electrolytes in the blood. Before hemodialysis can be performed, a surgeon must make a way for the blood to be pumped out of the body and then be returned after it has been cleansed. To do this, the surgeon uses an artery and a vein in the forearm. Arteries (which have muscles in their walls) bring oxygenated blood to the body from the heart, and veins return blood to the heart, which needs to have oxygen. The surgeon connects the radial artery in the forearm to a large vein called the cephalic vein. This connection is called an arteriovenous shunt. A shunt carries something from one place to another. In this case it carries blood from an artery to a vein. After this shunt is made, the veins in the forearm get big and eventually form muscles in their walls like arteries. They are now strong and can be punctured many times for dialysis.

Once the patient has a shunt, it is possible to connect the patient to the dialysis machine. A dialysis machine has three different parts. They are the tubes to get the blood to the machine, special filters (membranes) through which the blood passes, and a special solution called dialysate.

To begin dialysis, the patient's shunt is punctured on the arterial side and the venous side with two different needles connected to a set of tubes. The blood is pumped to a dialyzer by a roller pump through lines that can measure flow (how fast the blood is moving) and pressure. Heparin is added to the blood to keep it from clotting, and then the blood starts to flow into a special filter that functions like a semipermeable membrane. This membrane is surrounded by the special fluid dialysate, a solution of salt-water with sugar (glucose) and electrolytes. (Electrolytes are ions—molecules with an electrical charge—dissolved in the fluids of cells. They are responsible for regulating cell functions. The most important ones are sodium, potassium, chloride, and bicarbonates.)

The dialysate also has bicarbonate in it to make it similar to body fluids. Blood travels through this membrane in one direction, and the dialysate

is pumped around the membrane in the other direction. As the blood passes through this semipermeable membrane, all of the nitrogen wastes in the blood go into the dialysate, which is drained once it has been used. There are also higher levels (concentrations) of electrolytes like potassium and sodium in the blood. A lower concentration of electrolytes, the amount that should be in the blood, is used in the dialysate.

As osmosis takes place, electrolytes in the higher concentration (the blood) move to an area of lower concentration (the dialysate). Before the cleansed blood is returned to the patient, protamine, which deactivates heparin, is added. Most patients have to stay connected to the machine for about three or four hours, three times a week.

Peritoneal Dialysis

The other kind of dialysis is called peritoneal dialysis. The inside of the abdomen is lined with layers of cells called the peritoneum. The peritoneum acts like a semipermeable membrane. After a special tube, called a dialysis catheter, is placed in the abdomen, dialysate fluid (saltwater combined with sugar and electrolytes) is put inside the abdomen and allowed to stay there for several hours. During this time, the waste products from the blood diffuse by osmosis into the dialysate. This fluid is then drained off, and fresh fluid is added. Since this kind of dialysis takes longer, the patient has to do it several times a day, every day.

[*See also* **Artificial kidney**]

Dick test

The Dick test is a laboratory test designed to indicate whether or not a person is immune to (will not get) scarlet fever. Scarlet fever is a childhood disease. It derives its name from the flushed face, red rash and fever that it causes. The Dick test is named after George Dick and Gladys Dick, American bacteriologists who worked on the diagnosis and treatment of scarlet fever in the 1920s.

The Dick test involves administering two different injections, one into each arm of a patient. In one arm, toxin (poison) taken from a culture of scarlet fever bacteria is injected. In the other arm, neutralized toxin is injected to act as a control (a standard of comparison). If the toxin causes redness, tenderness and swelling after 24 hours, the person is not immune to scarlet fever. The control normally shows no swelling for comparison.

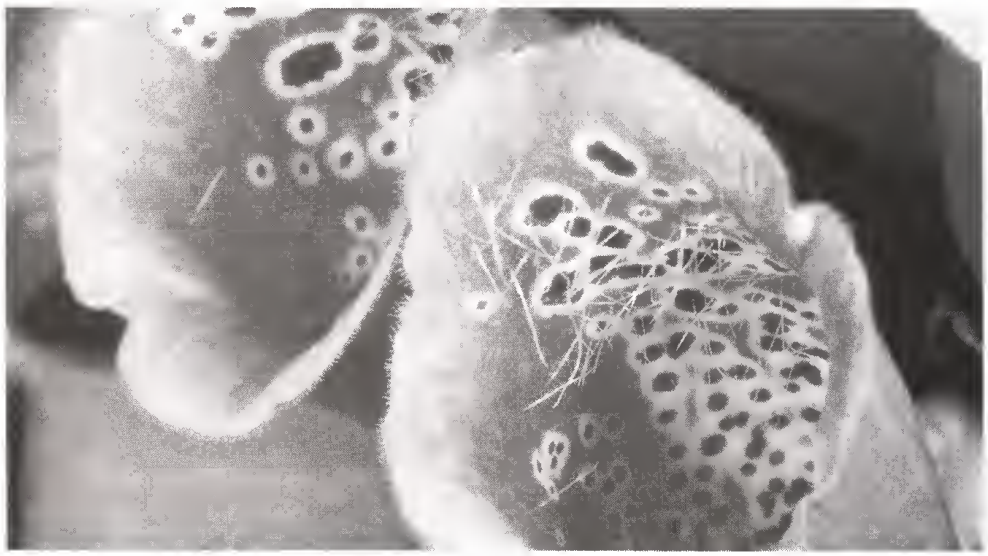
George and Gladys Dick obtained a British patent for their test in 1924 and a U.S. patent in 1925. The patents were for isolating the streptococcus bacteria that causes scarlet fever and for the preparation of an antitoxin for its treatment. Armed with the test and the antitoxin, doctors could diagnose and treat the disease much more efficiently. This resulted in a decline in the number of cases. Once **antibiotics** became more widely used, the incidence of scarlet fever became fairly uncommon.

[*See also* **Antibiotic**]

Digitalis

Digitalis is one of the most useful drugs in treating heart disease. It works by making the heart's contractions stronger without causing it to beat faster and become overworked.

Doctors often treat illnesses with drugs derived (obtained) from special substances found in plants. One of the most important of these drugs is digitalis, which is used to treat congestive heart failure. This heart condition occurs when the heart becomes enlarged and loses some of its effectiveness in pumping blood. Swelling caused by an accumulation of fluid in the arms and legs or hands and feet may be a sign of congestive heart failure. As long ago as the thirteenth century, people who used "folk" remedies began to notice that a plant commonly known as foxglove produced a medicine that could be used to treat some types of this swelling, called "dropsy." The medical term for swelling caused by a buildup of fluid is edema. Digitalis is one of the most useful drugs in treating heart disease. It works by making the heart's contractions stronger without causing it to beat faster and become overworked. This results in a slower, more effective heartbeat with longer periods of rest for the heart in between.



Digitalis. Digitalis is one of the most famous medicines derived from a plant.

The Pharmacy in the Garden

Other drugs used today that come from plants include tubocurarine, a surgical **anesthetic** derived from the **curare** vine; ephedrine, the active ingredient in decongestants, found in the stem of a Chinese shrub called mahuang; the **opium** poppy, which contains more than 20 alkaloids, of which **morphine, codeine,** and heroin are the most well known; **aspirin,** a painkiller derived from willow tree bark; reserpine, an anti-hypertensive that comes from the snakeroot plant; atropine, an intestinal (smooth muscle) antispasmodic and pupil dilator found in belladonna (deadly nightshade); and physostigmine, a glaucoma treatment and atropine poisoning antidote (remedy) derived from the Calabar bean.

Foxglove

Common foxglove is grown in gardens as a popular flower and also grows wild along roadsides and in meadows or logged areas, mainly in the western United States. The botanical name for common foxglove is Digitalis purpurea. Foxglove was brought to the United States by European migrants centuries ago. The plant has tube-shaped, spotted, purple flowers and grows to about five feet tall, with many large, thick, hairy leaves at the base of a tall stem. The variety grown in gardens varies in color from white to a deep rose.

Digitalis is one of the most well known medicines derived from a plant. Today scientists are searching in jungles and tropical rain forests for other plants that may contain substances to cure cancer, hepatitis, AIDS, and other serious diseases. Native medicine healers have used plants to treat illnesses among their people for thousands of years, and scientists today are working with modern-day medicine men in hopes of finding new wonder drugs among the earth's fast-disappearing natural resources.

Withering's Studies

In 1775 an English doctor named William Withering (1741-1799) began studying the foxglove plant. He learned that an effective medicine for treating heart ailments could be made from drying leaves picked just before the plant blossomed and crushing them into a powder. Withering also discovered that this medicine, digitalis—one of a number of substances called found in the plant—could be poisonous if the patient was given too much. Withering was aware that digitalis was effective only in

certain forms of dropsy (edema), but apparently did not associate this with the cardiac actions of the drug. Withering published his findings about digitalis in 1785, but in spite of his warnings about proper dosage, many doctors prescribed the medicine in doses that were too large and for sicknesses it could not cure.

The active principles of digitalis were not known to researchers until the mid-1800s, when two French scientists, Homolle Ouevenne and Theodore Ouevenne, found the substance digitalin in the foxglove plant. In 1875 Oscar Schmiedeberg (1838-1921) identified the potent chemical digitoxin in the plant, and in 1930 the English chemist Sydney Smith obtained the medicine used today, digoxin, from the wooly foxglove plant, Digitalis lanata.

Today doctors know that if too much digitalis enters the circulatory system the patient may experience nausea, vomiting, trouble with vision (seeing too much yellow or green), and a very slow and irregular heartbeat. A larger amount of digitalis can result in convulsions (severe seizures) and death. Even grazing animals that eat too much of the foxglove plant can become poisoned by its glycosides.

DPT vaccine

The DPT vaccine is one type of preventive medicine called immunization (to make things resistant to disease). The vaccine causes the body to form protective antibodies (disease-fighting proteins) against three serious diseases: diphtheria, pertussis (whooping cough), and tetanus (lockjaw). DPT is given in the form of an **inoculation** (shot or injection) in three separate doses about two months apart, with a "booster" shot one year after the primary series of inoculations is completed.

In the United States the DPT vaccine is usually given to babies during their first year of life because diphtheria and whooping cough tend to strike young children, are highly contagious, and can be fatal. A second booster shot is given at age four to six. Tetanus, or lockjaw, is an often-fatal disease that can strike persons of any age, but it can be prevented through immunization and supplementary booster injections every five to ten years.

Immunization is the best way to fight these and many other diseases. Many states in the United States have passed laws that say children cannot be enrolled in schools or day care centers unless they have been immunized against diphtheria, whooping cough, and tetanus. They must also

have been immunized against polio and measles, mumps, and rubella (German measles). The polio vaccine is given orally (by mouth), and the measles, mumps, and rubella (MMR) vaccine is combined into a series of injections, like the DPT vaccine.

Diphtheria

Diphtheria is a disease of the respiratory system caused by the bacterium "Corynebacterium diphtheriae." It mostly affects children and causes grayish white or yellowish mucous (slimy) coatings to form in the passages of the nose and throat. These "false membranes" can block the air passages, and surgery may be necessary to help the patient breathe. Bacteria enter the body through the mouth and nose and multiply, giving off a powerful toxin (poison). This toxin can damage the kidneys, heart, and central nervous system, leading to death.

Diphtheria is spread from person to person by coughing and sneezing and is more common among poor populations living in crowded conditions. In the late 1800s, before the development of a diphtheria antitoxin (a medicine to counteract the effects of the toxin), diphtheria killed thousands of people—especially children—in Europe and the United States.

German physician **Emil von Behring** (1854-1917) and Japanese scientist **Shibasaburo Kitasato** (1852-1931) were the first researchers to develop an antitoxin vaccine against diphtheria in about 1890. German microbiologist Paul Ehrlich (1854-1915) developed standard dosages for the antitoxin. In 1891 pathologist Anna Wessels Williams found a stronger strain of diphtheria antitoxin. In 1894 French bacteriologist Pierre Roux (1853-1933) developed a diphtheria antitoxin serum that he used to successfully treat more than 300 cases of the disease.

In 1913 Hungarian scientist and pediatrician Bela Schick (1877-1967) introduced the **Schick test**, which tells whether or not a person can get diphtheria if exposed to it. In the test a small amount of diphtheria toxin is injected under the skin. If a red, swollen rash develops, the person is susceptible to diphtheria and should be immunized.

Whooping Cough

Whooping cough, or pertussis, is a very contagious respiratory disease that causes patients to cough violently. After a series of coughs, the patient draws a deep breath that makes a whooping sound. Whooping cough is mainly a childhood disease and can be fatal, especially to infants.

Although whooping cough had been identified for at least a thousand years, it was not named until 1675 by English doctor Thomas Sydenham (1624-1689). Belgian scientists Jules Bordet and Octave Gengou discovered the bacillus that causes whooping cough in 1906. They developed a vaccine against the disease, but it did not work very well and whooping cough continued to infect thousands of children every year in the United States alone. It was through the work of three female scientists—Dr. Pearl Kendrick, Dr. Grace Eldering, and Dr. Margaret Pitman—that a potent whooping cough vaccine was developed in the first half of the twentieth century. Dr. Kendrick continued to make sure that the whooping cough vaccine being given all over the world was strong enough to prevent the disease. The vaccine is now given with diphtheria and tetanus vaccines to infants worldwide.

Tetanus

Tetanus is a serious infectious disease of the nervous system that causes severe contraction of the muscles. It is also known as lockjaw because spasms of the cheek muscles (tetany) make it nearly impossible to open the jaws. The muscle spasms caused by tetanus can spread to other muscles in the body, eventually making breathing difficult and resulting in death.

Tetanus is caused by a bacterium called Clostridium tetani that lives in soil and gets into the body through deep puncture wounds, burns, or crushing wounds in which there is much tissue damage. The tetanus bacilli multiply, releasing exotoxin (a poison) into the surrounding tissues. About 60 percent of the cases of tetanus are fatal, but immunization is an effective tool in the prevention of tetanus.

Behring and Kitasato also produced an antitoxin for tetanus. Behring later developed a toxin-antitoxin vaccine against tetanus. In 1893 Roux found a way to improve the procedures for using antitoxin serum to prevent as well as treat tetanus.

Today's tetanus vaccine is a toxoid (a form of tetanus toxin chemically treated so that it is nontoxic) that stimulates the growth of antibodies to the disease. In addition to the DPT vaccine series and booster shots, a person who suffers a dangerous wound that could be contaminated by the tetanus bacterium is often given two tetanus inoculations at the time of the injury. One is called tetanus immunoglobulin (Hypertet), which gives immediate immunity (by means of preformed antibodies already produced in a laboratory). The other is called tetanus toxoid, which stimulates the body's own defense system to make tetanus antibodies in about two weeks.

Ehrlich, Paul

Through his comprehensive study of the effects of chemicals in the human body, Paul Ehrlich (1854-1915) fathered the fields of **chemotherapy** (the treatment of disease with chemical agents) and hematology (the study of blood). He also made important contributions to the understanding of immunity and discovered Salvarsan, the first effective treatment for syphilis.

Ehrlich was born in 1854 in Strehlen, Germany, to a prosperous Jewish family. His interest in biology and chemistry led him to study medicine. He attended universities in Breslau, Strasbourg, Frieberg-im-Briesgau, and Leipzig, earning his medical degree in 1878. Ehrlich was fascinated by the reactions of cells and tissues to dyes. He developed new ways of staining cells to identify different types during his research.

Paul Ehrlich.

In 1890, Ehrlich became a professor at the University of Berlin, where he worked with **Emil von Behring** (1854-1917) and **Shibasaburo Kitasato** (1852-1931) on the study of the immune system (the body's method of fighting disease). The group searched for a substance that would give immunity against diphtheria (an infectious disease that effects the air passages) using antitoxins (natural antibodies). Ehrlich worked on the chemical aspects of the study and, in 1892, announced the develop-

ment of a diphtheria antitoxin for medical use. He shared the 1908 Nobel Prize in medicine with Soviet biologist Elie Metchnikoff (1845-1916) for their work on immunity and serum therapy.

In 1894 Ehrlich was made director of a new institute for serum research in Frankfurt, Germany, where he studied the concepts of active and passive immunity. Ehrlich also continued his study of blood using staining techniques. Realizing that stains colored bacteria but not surrounding cells, he looked for a way to combine the stain with a substance that could kill the bacteria. He did identify dyes, such as trypan red, that had the ability to destroy microorganisms on their own.

Ehrlich began working with organic compounds containing arsenic because he thought its properties were similar to those of the nitrogen atoms that gave trypan red its effectiveness. He studied literally hundreds of arsenic compounds. By 1907, he had reached number 606, which he put aside because it was not effective against trypanosomes. However, two years later, Ehrlich's assistant, Sahachiro Hata (1872-1938), discovered that compound number 606 was effective against the fatal, sexually transmitted disease of syphilis. Triggered by a microorganism called a spirochete, syphilis causes the nervous system to break down, eventually leading infected people to experience intense pain and insanity prior to death. In 1910 Ehrlich announced that chemical 606, which he called Salvarsan, could cure syphilis.

For several years Ehrlich suffered personal and professional attacks because of his work with syphilis. Some people felt that the disease was a punishment for sinful sexual behavior and attacked Ehrlich for searching for a cure. The administration of the drug was also complicated, even risky at first, and when a few patients died because doctors administering the drug failed to follow Ehrlich's instructions, he was accused of fraud. The attacks finally ceased in 1914 when the German parliament finally endorsed his cure as authentic. Unfortunately, the strain surrounding his controversial efforts to cure syphilis took its toll on his health and he suffered a series of strokes during his last year which led to his death in Bad Homburg, Germany, in 1915.

[*See also* **Antibiotic**]

Eijkman, Christiaan

Christiaan Eijkman (1858-1930) discovered that not all diseases were caused by microorganisms like bacteria and viruses, but that some were

due to dietary deficiencies, particularly deficiencies of certain **vitamins.** Born in the Netherlands in 1858, Eijkman received his medical degree from the University of Amsterdam in 1883, then went to Germany to study under the famous bacteriologist, **Heinrich Robert Koch** (1843-1910). Encouraged by Koch, Eijkman joined a commission sent to the Dutch East Indies (now Indonesia) in 1887 to investigate the disease beriberi and begin the work that was to make him famous.

Beriberi Research

At the time, beriberi was a widely prevalent disease, characterized by polyneuritis, the kind of nerve damage that causes numbness, paralysis and in many cases, death. Because **Louis Pasteur's** germ theory of disease had already led to so many successful cures, physicians now assumed that all diseases must be caused by microorganisms. But the scientific commission found no microorganism that caused beriberi. Disappointed, most of the group returned home in 1887, but Eijkman remained behind to serve as director of a new bacteriology lab set up in a medical school constructed for native doctors. It was there that around 1890 Eijkman helped solve the problem of beriberi, partly by accident.

When a group of laboratory chickens suddenly developed a strange disease—one with symptoms that resembled polyneuritis—Eijkman promptly commandeered the chickens and once again tried to find the causative germ, without success. Moreover, he was unable to transfer the disease from sick chickens to healthy ones. To add to his frustration, the disease vanished as suddenly as it had started.

Fortunately, Eijkman refused to give up. He stubbornly continued to try to figure out this peculiar vanishing disease. Before long, he learned that, for a brief period of time, one of the cooks had been feeding the lab chickens boiled rice from the hospital's own stores. A second cook, however, decided it was wrong to feed rice meant for people to mere chickens, and switched back to cheaper unpolished rice. Oddly enough, Eijkman learned that the chickens had developed their illness while eating the polished rice. To determine whether the polished rice was actually responsible for causing the sickness, Eijkman began feeding it to other chickens which quickly developed the beriberi-like illness. Eijkman could then cure this new illness by switching the sick chickens back to unpolished rice.

Eijkman had discovered a dietary deficiency disease. At first, he did not fully understand the meaning of his findings, assuming that there must be a toxin (poison) in rice grains that could be neutralized by something in the hulls. But others would quickly clarify his results. A younger colleague, Gerrit Grijns, took over the nutrition studies when an illness forced Eijk-

man to go home in 1896. In 1901 Grijns proposed that beriberi was caused not by germs, but by the lack of some natural substance present in rice hulls and other foods (this substance turned out to be **thiamine**, a vitamin. Over the next decade, a number of investigators—most notably, England's **Frederick Gowland Hopkins** (1861-1947)—came to similar conclusions about a number of diseases and a new era in medicine was launched. Eijkman, whose work served as the basis for the modern theory of vitamins, shared the Nobel Prize in medicine with Hopkins in 1929.

Electrocardiograph (ECG)

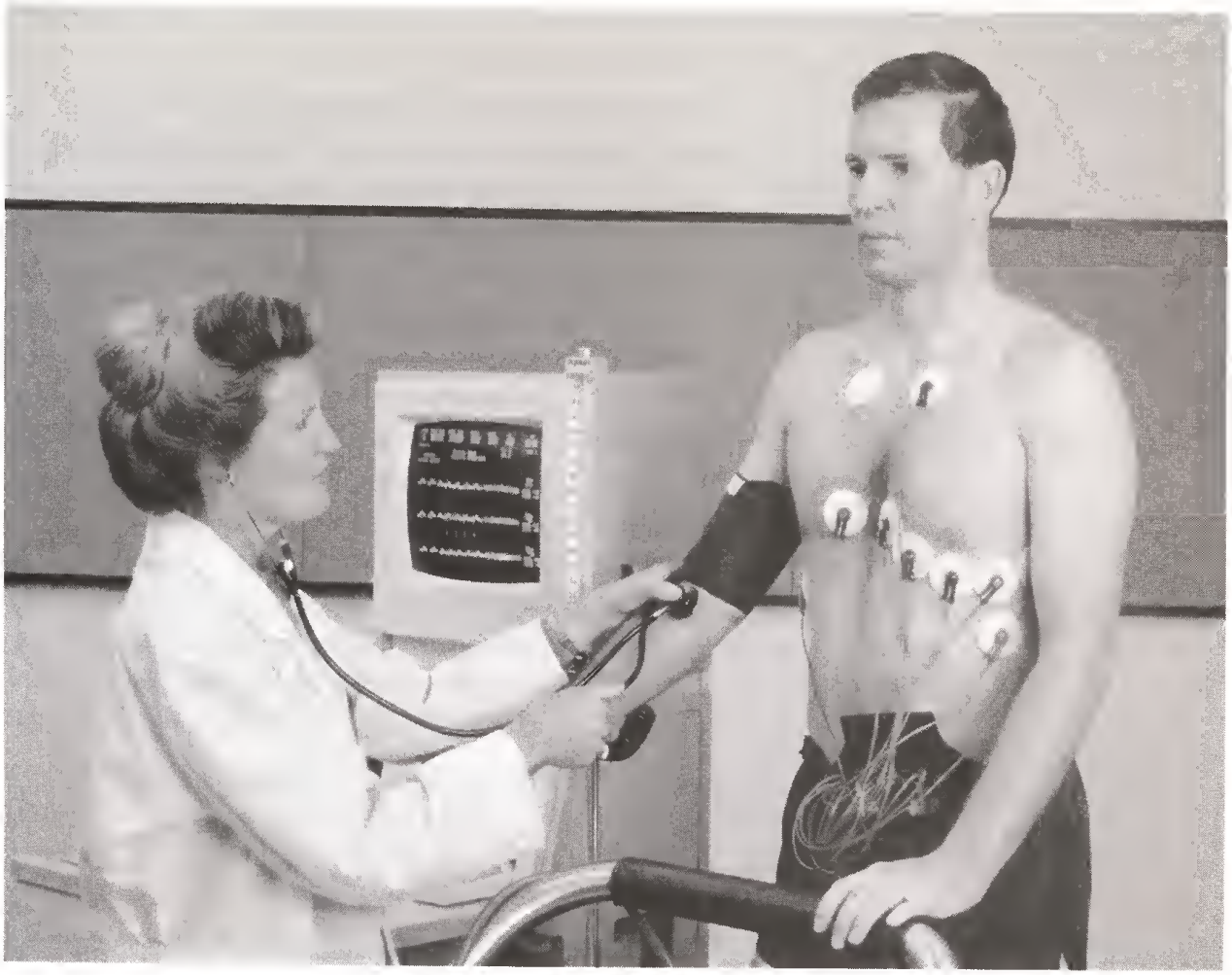
In the late 1700s medical researchers learned that muscular contractions produce tiny electric currents. Research scientists reasoned that a recording of the electric impulses of the heart could reveal irregularities and, hence, heart disease. The Italian biophysicist Carlo Matteucci (1811-1868) observed electric impulses from a pigeon's heart in 1843. In 1856 the German scientists Rudolf Albert von Kölliker (1817-1905) and Heinrich Müller (1820-1864) recorded electric currents produced by a frog's heart.

The Measuring Device

Researchers attempted to develop accurate measuring devices. French physiologist Augustus Waller (1856-1922) found that cardiac currents could be recorded by placing surface electrodes on the body. Waller used a capillary electrometer. This device consisted of tubes of mercury that rose and fell with the changes in heart muscle current.

Dutch physiologist Willem Einthoven (1860-1927) set out to design an improved apparatus and in 1903 he described the results, a string galvanometer. The galvanometer consisted of a thin silver-coated quartz wire stretched between the poles of a magnet. As electric current flowed through, the wire was deflected. The magnified motion was projected onto moving photographic film. The extreme sensitivity of the device allowed it to detect the tiny cardiac currents very accurately.

Einthoven called his machine the electrocardiograph and the recorded electrical impulses an electrocardiogram. He devised the standard positioning of the electrodes on the human body. He also described the regular heart waves and the method used to interpret electrocardiograms. Through clinical studies, Einthoven identified a number of heart problems



An modern electrocardiograph exam. Electrocardiography permits diagnosis of heart conditions without needles or incisions.

with his galvanometer. English physician Sir Thomas Lewis (1881-1945) established the electrocardiogram as a standard clinical tool.

With refinements in instrumentation and technique, electrocardiography became one of the most useful diagnostic tools in medicine. It is highly accurate, easy to interpret, and relatively inexpensive. Electrocardiography permits diagnosis of heart conditions without needles or incisions, and has pointed the way to similar diagnosis of brain currents.

Electroencephalogram (EEG)

An electroencephalogram (EEG) is a graphic (vivid) picture of the electrical activity of the brain. An EEG is made by placing electrodes (small terminals which conduct an electrical current) on the subject's scalp and

connecting the electrode wires to a machine known as an electroencephalograph. The electroencephalograph then records the patterns of brain waves (rhythmic changes in the electric impulses of the brain.)

EEGs are used to diagnose epilepsy (a disorder marked by severe seizures or convulsions), brain tumors, strokes, and other neurological (nervous system) conditions. These conditions are characterized by distinctive, abnormal patterns of brain waves. EEGs are also used in investigating psychiatric disorders, such as schizophrenia (a psychiatric condition in which a person's sense of reality is severely distorted). In addition, EEGs help in defining brain death (the measurable end of brain activity). This diagnosis is necessary before the donation of organs for surgical **transplants.**

Making an Encephalogram

Hans Berger (1873-1941) was a German psychiatrist who developed the first human EEG in 1924. Berger was interested in psychophysiology (the study of the relationship between mental processes and the brain). Berger decided to measure the brain's electrical activity in the hope that the physiological record would provide insight into mental processes.

Berger began his search for the human EEG by experimenting with dogs. He moved on to humans and started placing needle electrodes under the scalp of patients who had lost some of their skull bones in surgery. It was while working with one of these patients that Berger recorded the first human EEG in 1924. At first, he was uncertain whether the oscillations (changes or variations) he had recorded originated in the brain. It was not until after he had conducted many other experiments that he published his first paper on the human electroencephalogram in 1929.

The initial reaction of others to Berger's work was one of disbelief. The scientific world doubted whether the workings of an organ as complex as the brain could be recorded through the skull. Berger did not achieve an international reputation until 1934. It was then that Edgar Douglas Adrian (1889-1977), a renowned English neurophysiologist (one who studies the functions of the nervous system), confirmed Berger's findings.

BEAM Enhances the Value of the EEG

Since the time of the original study, research scientists have used the EEG to identify the sources of brain activities. They have located the parts of the brain involved in the mental processes of reasoning, memory, and feeling. Interpreting the EEG was made easier in the 1980s with the use of the BEAM (brain electrical activity mapping) system. This system was invented by Frank Duffy of the Harvard Medical School. It uses com-

puter technology to combine the signals from the individual electrodes into a overall, color-coded map of the brain's electrical activity.

Using the computer, BEAM can handle a wide range of tasks. It can store large amounts of EEG data, compare healthy profiles with abnormal ones, and provide detailed analyses. These analyses have been used to accurately diagnose such conditions as dyslexia (a condition marked by a difficulty with reading) and schizophrenia. Both of these conditions are usually difficult to detect.

The Future of BEAM

Efforts are currently underway to use BEAM in matching EEG patterns to specific brain functions. For example, research scientists have used BEAM to map the electrical activity involved in the movement of a monkey's arm. The studies have shown that when the monkey anticipates moving its arm, the pattern of electrical activity in its brain changes. If efforts like these are successful, it may one day be possible to use computers and the electrical activity of the brain to control the movement of **artificial limbs.**

[*See also* **Artificial limb and joint; Transplant, surgical**]

Embryonic transfer

Embryonic transfer is the moving of a fertilized egg that is between two and eight weeks old from the womb of one woman to the womb of another. The first successful human embryo transfer occurred in 1983. The transfer resulted in the birth of a live child.

Animal Research

English doctor Walter Heape performed a successful embryo transfer in 1890. He removed embryos from a female rabbit and placed them into a female hare (a hare is related to the rabbit), that subsequently gave birth. Further experiments were carried out on 15 different animal species. Embryo transfer became a valuable technique in the cattle industry. Superior animals could produce large numbers of embryos. These embryos could then be carried by less valuable cows. For example, a cow that was a good milk producer could produce the embryos that could them be implanted into cows that were poor producers. This way, more cattle with the desired traits could be raised by a number of different mothers.

Human Embryo Transfer

Human embryo transfer got its start in 1972. A Chilean team led by Horacio Croxatto developed a technique for flushing an unimplanted, unfertilized egg out of the uterus. The brothers Randolph Seed, a surgeon, and Richard Seed, the head of a cattle-breeding company, used a similar technique in 1980 to recover a fertilized egg. The brothers founded a company called Fertility and Genetics Research. This company funded a medical team at Harbor-UCLA Medical Center in Torrance, California.

The team began treating a group of infertile women, and advertised for egg donors. Healthy donors were matched with recipient couples for blood type, Rh, and hair and eye color. As each donor reached readiness for ovulation, she was inseminated with the husband's sperm. The fertilized egg was recovered and then transferred to the uterus of another woman. Two transfers performed by the team in 1983 resulted in the birth of babies early in 1984.

Embryo transfer is a valuable technique for overcoming infertility in women. It carries risks of infection for both donor and the recipient. It also carries the risk of unwanted pregnancy for the donor if the embryo implants in the uterine wall before it can be removed.

[*See also* **In vitro fertilization**]

Enders, John Franklin

John Franklin Enders (1897-1985) was born in Connecticut and graduated from Yale University in 1920. After beginning a career as a real estate agent, Enders decided that business was not for him. He enrolled at Harvard University, completing a master's degree in English literature. While pursuing further graduate studies, a roommate introduced him to Hans Zinsser (1878-1940), a well-known microbiologist who was head of Harvard's Department of Bacteriology and Immunology. Zinsser's enthusiasm for scientific pursuits was so contagious that Enders abandoned his liberal arts studies in favor of medical research.

After receiving a doctorate from Harvard in 1930, Enders began research on how the immune system fights bacterial disease. In 1937, however, he became intrigued with the problem of viruses, a much smaller microorganism. During this time, the study of viruses was restricted by microscopes not powerful enough to see these small organisms, and by the fact that viruses can grow only in live tissue. The live tissue problem led

Enders to work in the improving tissue culture techniques to provide material for vaccines.

World War II (1939-1945) interrupted his work. By 1947, however, Enders, Thomas Weller and Frederick C. Robbins, (Weller's medical school roommate) were at Children's Hospital in Boston, Massachusetts, growing the mumps virus in cultures of chicken cells. Weller had been working on chicken pox viruses while Robbins was trying to isolate the virus that causes infantile epidemic diarrhea. Together, this team developed better tissue cultures for mumps, chicken pox, polio viruses.

Techniques the three researchers developed for the growing polio virus were essential to the later development of the life-saving vaccines of **Jonas Salk** and **Albert Sabin**. For this innovation, Enders, Weller and Robbins received the Nobel Prize for medicine in 1954. Enders continued working in the area of virus cultures and successfully grew the measles virus which was used in the first measles vaccine. After retirement from Harvard, Enders kept an active interest in virology and at the time of his death was studying the AIDS virus.

Endorphin and enkephalin

Endorphin and enkephalin are the body's natural painkillers. When a person is injured, pain impulses travel up the spinal cord to the brain. The brain then releases endorphins and enkephalins. Enkephalins block pain signals in the spinal cord. Endorphins are thought to block pain principally at the brain stem. Both are **morphine**-like substances whose functions are similar to those of **opium**-based drugs.

Today, the word "endorphin" is used generically to describe both groups of painkillers. These naturally occurring opiates include enkephalins (methionine and leucine), endorphins (alpha, beta, gamma, and delta) and a growing number of synthetic (artificial) compounds.

Natural and Artificial Painkillers

In the mid-1960s scientists proposed theories that the opiate narcotics (opium, heroin, morphine) mimic the actions of naturally occurring chemicals within the brain. They believed that these narcotics act as painkillers by manipulating the brain's receivers for those naturally occurring substances.

In the late 1970s researchers learned that there are specific areas in the brain that control pain. It is those areas that opiates attach themselves to in order to perform their functions. It was only then that researchers were able to identify the two naturally occurring pain killers, endorphins and enkephalins. This offered opportunities for developing drugs similar in structure to the natural pain-killing substances.

[*See also* **Morphine; Opium**]

Endoscope

Endoscopes are primarily used in the health care field, but can also be used for industrial purposes. Endoscopes make it easier to examine hard-to-reach places such as the inside of fuel tanks and nuclear reactors

An endoscope is an instrument that allows doctors to view the inner workings of the human body without having to perform surgery. Endoscopes are sometimes called fiberscopes. Endoscopes are primarily used in the health care field, but can also be used for industrial purposes. They make it easier to examine hard-to-reach places such as the inside of fuel tanks and nuclear reactors.

The endoscope is a flexible narrow tube. It contains several bundles of hair-thin glass fibers covered with a reflective coating. An intense light source, usually a halogen lamp, is part of the instrument. The light is transmitted along one bundle of fibers toward the target area and provides enough light to see inside of the human body. Another bundle of fibers carries an image of the target area back up the tube where it is viewed through an eyepiece.

Early Endoscope Research

Crude versions of the endoscope were used as early as the nineteenth century and included long, rigid tubes illuminated by candles. In 1854 Manuel Patricio Rodriguez Garcia, a Spanish-born vocal teacher, designed the forerunner of the laryngoscope that allowed a clear view of the glottis (the vocal cords and the opening between them) and made it possible to see obstructions in the larynx.

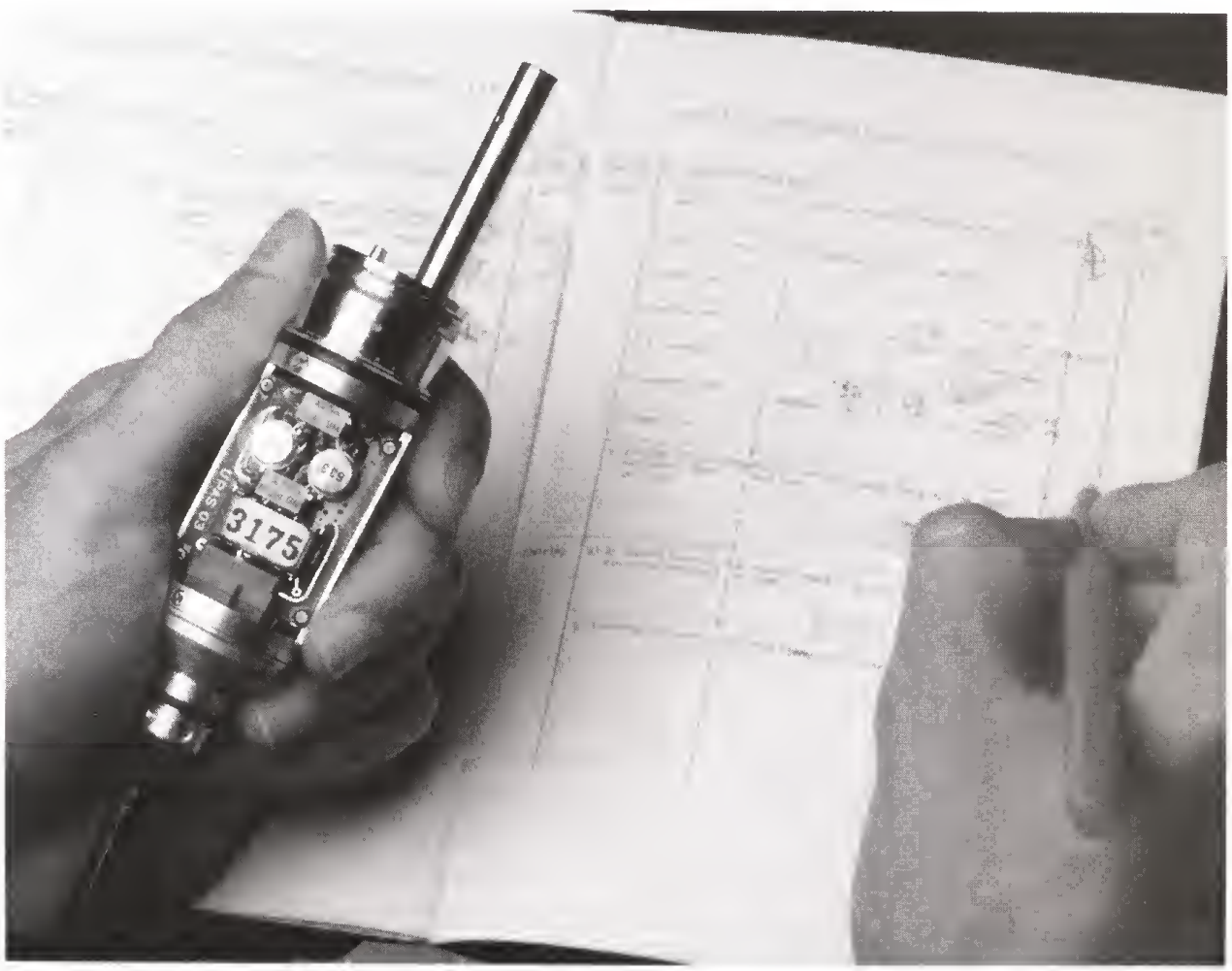
The first efforts to develop the kind of glass fibers that would eventually be used in endoscopes were made by the Atomic Energy Authority and by the Rank Organization in Britain. By 1965, a 25-micron (a micron is one-thousandth of a millimeter) fiber had been produced. An American company, Bausch and Lomb, subsequently developed a 15-micron fiber for their Flexiscope which could be used for industrial inspections because it gave off a "cold" light that was safe even in fuel tanks. When the Amer-

ican Cytoscopic Company succeeded in sterilizing glass fibers, the possibilities for medical uses of the endoscope increased greatly.

Medical Uses

The modern endoscope can perform an amazing variety of medical procedures. It can do much more than transmit light and a visual image. It also contains water and air channels for flushing water through or inflating targeted areas.

Tiny forceps (tweezers) can be placed at the tip of the endoscope. These can be used to take specimen samples for laboratory analysis and to perform simple operations such as removing colon polyps or gallstones. Endoscopes can also be used to stop hemorrhaging (heavy bleeding) by delivering laser beams directly to the point of bleeding. The blood thickens and the bleeding is stopped.



An modern endoscope and printout. Crude versions of the endoscope were used as early as the nineteenth century.

Different types of endoscopes are specially designed to examine specific parts of the body. Angioscopes pass through the arteries that carry blood to the heart, **arthroscopes** explore the interiors of joints, bronchoscopes are used with a special dye and fluorescent light to detect lung malignancies (cancers), gastroscopes probe the stomach and upper intestinal tract, and laparoscopes diagnose and treat abdominal conditions.

Enzyme

Enzymes have been called the "agents of life" because all life processes are dependent on them. Enzymes are protein molecules that act as catalysts (they speed up chemical reactions without undergoing any change themselves). They can build up or break down other molecules and are responsible for regulating the many chemical reactions that occur in plants and animals. If enzymes were absent from the human body, most of its metabolic reactions would occur at a rate, too slow to support life.

Enzymes accelerate reactions by at least a million times. Molecules in the cells of solid tissues and in circulating blood are constantly being split apart and welded together again by enzymatic action. It has been estimated that a single cell, roughly one-billionth the size of a drop of water, contains about 3,000 different enzymes.

Regulatory Functions

In addition to speeding up reactions, enzymes also have regulatory functions. It is essential that chemical reactions inside cells are controlled so that they do not make too little or too much of a particular product. Many of the processes, or pathways, in cells must be coordinated, and this is a function enzymes regulate. Enzymes are thus central not only to individual reactions within a cell but also to the life of the cell as a whole.

Enzymes are critical to the proper functioning of everything from breathing to thinking to blood circulation to digestion. They can be broken down into two major groups, metabolic enzymes and digestive enzymes. Metabolic enzymes are produced by the body to regulate functions in the blood, tissues, and organs. Digestive enzymes are produced to break down food and absorb nutrients.

Enzymes and Digestion

Prior to the eighteenth century, the process of digestion was believed to be solely a mechanical process, similar to a meat grinder. In 1752, however, French scientist René-Antoine Réaumur fed his pet falcon pieces of meat enclosed in a metal tube with holes in it. He wanted to protect the meat from the mechanical effects of the bird's stomach friction. When he removed the tube a few hours later, the meat had been digested, but the tube was still intact. It was evident that the digestion had resulted from chemical, not mechanical, action. In the 1780s Italian biologist Lazzaro Spallanzani also proved that meat could be digested by gastric juices extracted from falcons. His was probably the first experiment in which a vital reaction occurred outside the living organism.

John R. Young, who graduated from the University of Pennsylvania in 1803, added to the increasing knowledge about digestion. In his graduation essay, he described his experiments on frogs and snakes and on himself. He was the first researcher to reveal that gastric juice contains a strong acid. Young believed that the strong acidity of gastric juice was responsible for its digestive action. In 1835, however, German physiologist Theodor Schwann discovered that gastric juice also contained a non-acid digestive substance. He called the substance pepsin (from the Greek for "to digest"), which was later shown to be an enzyme.

Fermentation

The oldest known enzyme reaction is alcoholic fermentation, which was thought to be a spontaneous reaction until **Louis Pasteur** (1822—1895) proved otherwise in 1857. Pasteur found that fermentation was caused by yeast cells digesting sugar for their own nourishment. In 1878 German physiologist Wilhelm Kühne (1837-1900) coined the term "enzyme," meaning "in leaven," to describe this process. The word enzyme was used later to refer to substances such as pepsin, and the word ferment was used to refer to chemical activity produced by living organisms.

In 1897 another German scientist, Eduard Buchner, discovered by accident that fermentation actually does not require the presence of living yeast cells. Buchner made an extract of yeast cells by grinding them and filtering off the remaining cell debris. Then he added a preservative—sugar—to the resulting cell-free solution to preserve it for future study. He observed that fermentation, the formation of alcohol from sugar, occurred. Buchner then realized that living cells were not required for carrying out metabolic processes such as fermentation. Instead, there must be some small entities capable of converting sugar to alcohol. These entities were

enzymes. Buchner's accidental discovery won him the 1907 Nobel Prize in chemistry.

After Buchner's discovery, most scientists assumed that fermentation and other metabolic reactions were caused by enzymes. All attempts to isolate and determine the chemical nature of enzymes were unsuccessful, however, until 1926. That year American biochemist James Sumner of Cornell University isolated the enzyme urease from the jackbean after nine years of research. The enzymes pepsin and trypsin were isolated four years later by the American biochemist John H. Northrop. It was later shown that enzymes are proteins. In more recent research, ribonuclease, a three-dimensional enzyme, was discovered in 1938 by the American bacteriologist René Dubos. The enzyme was synthesized by American researchers in 1969.

Enzymes in Medicine

Some diseases can be treated by using substances that inhibit (curb) enzymes. Inhibitors can be used to attack enzymes that are critical to the survival of an organism when such undesirable organisms as disease-causing bacteria or parasites pose a threat to health. Neostigmine, used to treat myasthenia gravis (a disease that causes severe muscle weakness), strongly inhibits the enzyme cholinesterase. L-asparaginase is believed to be a potent weapon for treating leukemia. And a class of enzymes called dextrinases are believed to be effective in preventing tooth decay.

Research is also being conducted into malfunctioning of enzymes, which may be linked to such blood disorders as diabetes and anemia. Geneticists have also discovered that in some hereditary diseases, such as phenylketonuria and galactosemia, the affected individuals are actually missing certain enzymes. Some of these enzyme-deficiency diseases can now be effectively treated, and many researchers are concentrating on the search for more of these disorders, which may ultimately revolutionize the practice of medicine.

[*See also* **Genetic engineering**]

Epinephrine

Epinephrine, also known as adrenaline, is a **hormone** secreted by the medulla (inner part) of the adrenal glands, located on the kidneys. The adrenal glands are one of the body's endocrine glands (glands producing substances that are distributed by way of the bloodstream).

Epinephrine was the first hormone to be discovered. Hormones are substances produced by body cells that circulate in body fluid and influence the activity of cells in another part of the body. In the 1950s, the American pharmacologist Earl Sutherland (1915-1974) discovered that epinephrine does not act directly on cells, but stimulates production of cyclic AMP, a second messenger that regulates cell activity.

Epinephrine was the first hormone to be discovered.

Epinephrine is produced continuously in small amounts by the adrenal glands, but when the body is threatened in times of excitement, danger, or emotional stress, the brain sends messages to the adrenal glands, which respond by increasing epinephrine production.

This increase in epinephrine stimulates the heart, raises blood pressure, constricts small blood vessels, releases sugar stored in the liver, and relaxes certain involuntary muscles while it contracts others. These changes in the body prepare it for "fight or flight," meaning the body is more alert, physically stronger, and has greater energy. The person is now better prepared to face the danger at hand (fight) or escape from the danger or stress (flight).

Early Research and Use

The power of adrenal extracts was first observed by the British physiologist Edward Sharpey-Schäfer (1850-1935). In 1894 he injected an adrenal extract into an experimental animal, causing its blood vessels to narrow and forcing an increase in blood pressure. Japanese American chemist Jokichi Takemine (1854-1922) isolated epinephrine in 1901, based on preliminary work done in 1897 by American pharmacologist John Jacob Abel (1857-1938).

Epinephrine was soon available for medical purposes such as reviving persons suffering from hemorrhage and shock. It was once prepared using adrenal glands of animals, but is now produced synthetically.

Hormones and the Body

In 1905 the British physiologists William Bayliss (1860-1924) and Ernest Starling (1866-1927) introduced the concept of a hormone, a substance that is produced by one organ and carried by the blood to another organ, where it influences its functions. Only then did scientists realize that epinephrine was a hormone.

The significance of epinephrine and other hormones in the body's operations was discovered by the American physiologist Walter Bradford Cannon (1871-1945), after he worked with injured World War I (1914-1918) soldiers. Other scientists had already studied the body as an inter-

nal environment and the interrelation of metabolism, hormones, and the immune system. In 1926 Cannon developed the concept of homeostasis (an organism's ability to remain stable internally, even when the surrounding environment exerts great stress upon it, such as hunger, thirst, and sudden danger). Homeostasis in turn led to such ideas as biofeedback (the interaction of internal and external signals and responses in the body).

Catecholamines

Epinephrine is one of several structurally related compounds in the body called catecholamines. These compounds help regulate the sympathetic nervous system, which is part of the autonomic nervous system. The autonomic nervous system helps the body maintain homeostasis. The autonomic nervous system makes rapid adjustments to changes in environment by freeing chemical agents that act as they are released.

The endocrine system acts more slowly by releasing agents over periods of hours or days. Because it releases hormones but acts so quickly, the adrenal medulla cannot be strictly classified as part of the nervous system or part of the endocrine system. The neurohumoral theory may explain how the two act as one in many cases.

Other catecholamines are norepinephrine (also called noradrenaline or levoarterenol) and dopamine. The general function of norepinephrine seems to be the maintenance of normal blood circulation. It is also the chemical agent that is responsible for transmission of nerve impulses in the sympathetic nervous system. When a person has certain tumors of the adrenal glands, large amounts of epinephrine and norepinephrine are produced, causing a great increase in blood pressure. Dopamine is also a nerve impulse transmitter.

Synthetic (synthesized) catecholamines are important in medicine as heart stimulants and vasoconstrictors (substances that cause blood vessels to narrow), as well as relaxants of the bronchial and other muscles.

Vasopressors

Epinephrine is one of the most powerful vasopressor (causing a rise in blood pressure) drugs known. It increases the strength of heart muscle contractions as well as the heart rate, and it constricts blood vessels and veins. Because it is a powerful heart stimulant, it is used in emergency medicine to restore heart rhythm in cases of shock and in certain cases of cardiac arrest (heart attack). The most common use of epinephrine in medicine is to relieve breathing distress in patients with asthma, bronchitis, and

emphysema. The synthetic catecholamine isoproterenol is also used in the treatment of these diseases.

Epinephrine is a powerful bronchodilator, meaning it relaxes bronchial muscle. It also constricts pulmonary vessels (in the lung), and inhibits the release of histamines triggered by allergic reactions. As a bronchodilator it is most often inhaled by mouth as a spray or through another breathing apparatus. Epinephrine is also used on the skin or mucous membranes to control bleeding of wounds because it constricts blood vessels. It is sometimes used for the same reason during surgery of the nose, throat, and larynx, where it also shrinks mucosa (membranes that secrete slime), making surgery easier.

Epinephrine increases metabolism, accelerates blood coagulation, and lowers pressure inside the eye in some types of glaucoma.

Ether

Ether is a colorless, transparent, and very volatile (readily vaporizable) liquid. It has a characteristic odor and is highly flammable. Ether is used as a general anesthetic for surgery.

Ether (from the Latin "aether" and the Greek "eithr," or "the upper and purer air") is believed to have been first synthesized about 1540 by German botanist and chemist Valerius Cordus (1515-1544), who called his discovery "sweet oil of vitriol" and praised its medicinal properties. Paracelsus (1493-1541), a contemporary of Valerius, noted that the "oil" induced sleep in chickens when added to their feed. Frobenius (Froben) named the liquid "ethereal spirits" or "ether" in 1730.

History of Surgical Anesthesia

Only a few surgical procedures were available before the mid-1800s. Little was known about diseases or how to prevent infection. There was also no satisfactory **anesthesia** available to put the patient into a deep sleep and allow doctors to perform unhurried operative procedures. Certain means of reducing surgical pain had been available since ancient times, however. These included such drugs as alcohol, hashish, and **opium** derivatives.

Also available were rudimentary physical methods of producing analgesia (insensitivity to pain). These included packing a limb in ice or applying a tourniquet. Another technique used, although an extreme one, was to induce unconsciousness, either by inflicting a blow to the head or by stran-

gulation. Most often, however, the patient was simply restrained by physical force, thus making surgery a last resort.

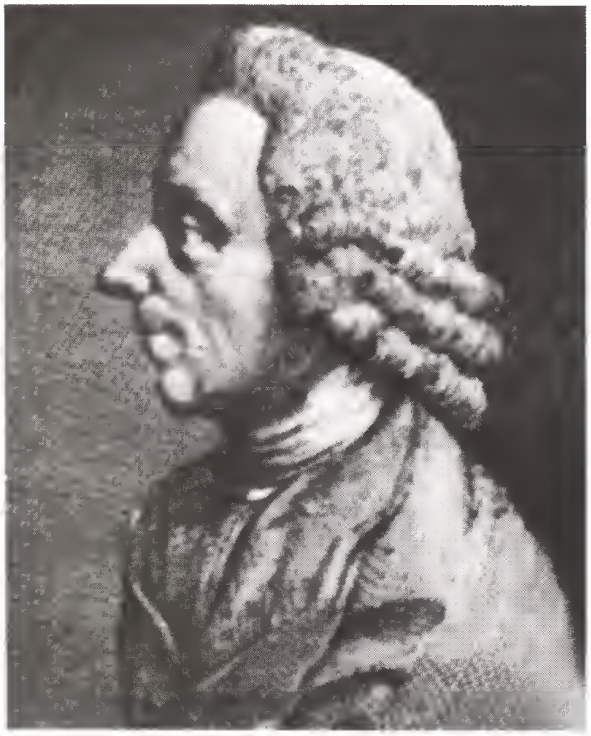
As more and more was learned about anatomy and surgical procedures, the need to find safe methods to prevent pain became more urgent. With the advent of professional dentistry, this need became even more urgent because of the sensitivity of the mouth and gums. Indeed, dentists were largely responsible for the introduction of both **nitrous oxide** and diethyl ether.

Nitrous Oxide and Anesthesia

In 1772 the English chemist Joseph Priestley (1733-1804) discovered nitrous oxide gas. Soon people, especially medical students, began to whiff this "laughing gas" at "revels" for social amusement and for the euphoria ("high") it produced. Ether "frolics," in which participants inhaled ether, also became popular in the United States.

Dr. Crawford W. Long (1815-1878) of Georgia may have been the first person to apply his social experiences with ether to surgery. A graduate of the University of Pennsylvania, Crawford is said to have observed a participant at a frolic take a heavy fall but show no indication of pain. In 1842 Long performed three minor surgeries using sulfuric ether, a form of ether with chemical properties similar to those of diethyl ether. Long apparently did not realize the medical significance of what he had done and failed to publicize his discovery. He published his results only after anesthesia had been hailed as a major breakthrough.

Joseph Priestley discovered nitrous oxide gas, a close associate of ether, in 1772.



Attention next returned to nitrous oxide. Horace Wells (1815-1848), a Hartford, Connecticut, dentist, learned about the effects of nitrous oxide in 1844. He decided to test the gas by having one of his own teeth removed while under the influence of the gas. He was delighted with the results and soon began using the gas on his patients. He also told his friend and former partner, William T. G. Morton (1819-1868), a student at Harvard Medical School, about his discovery.

Morton was interested in the possibilities of anesthesia but began to look for a more potent agent than nitrous oxide. He began experimenting with sulfuric ether. Pleased with the results in his dental practice, he contacted Dr. John C.

Warren (1778-1856) of Harvard University in 1946 and arranged for a public demonstration of surgery without pain. News of this event spread rapidly, and a new era for surgery began. Oliver Wendell Holmes later coined the term anesthesia to describe the condition brought on by ether.

The knowledge of ether as an anesthetic spread rapidly. The medical establishment and the public quickly and gratefully accepted the use of ether inhalation for painless surgery. Within months, surgery using ether anesthesia was being performed in England. In Germany Johann Friedrich Dieffenbach (1795-1847), a pioneer in plastic surgery, wrote: "The wonderful dream that pain has been taken away from us has become reality. Pain, the highest consciousness of our earthly existence, the most distinct sensation of the imperfection of our body, must now bow before the power of the human mind, before the power of ether vapor."

Other advances in anesthesia soon followed. In 1847 Russian Nicolai Ivanovich Pirogoff (1810-1881) devised a method of administering ether vapor via the rectum. Marc Dupuy investigated the same technique that year in Paris, France. In 1915 American surgeon George Crile began combining local anesthetics with ether inhalation to block pain impulses more completely.

Eyeglasses

Eyeglasses are corrective lenses mounted in frames. They are used to help people with vision problems see clearly. The lenses are shaped in order to bend light rays. This allows the rays to focus on the back of the eye, or the retina.

The Shape of the Eye

The need for eyeglasses is determined by the shape and condition of the eye itself. If the eyeball is too shallow, the image passing through the lens focuses behind the retina. When the eye is too deep, the image focuses in front of the retina. When the eye looses its elasticity it tends to focus the image behind the retina.

There are a number of different types of vision problems that can be corrected with eyeglasses. These conditions include:

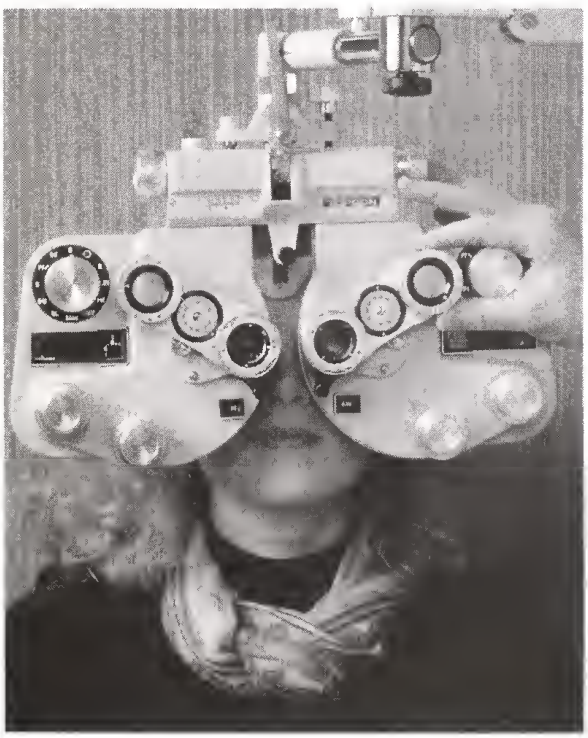
- Hyperopia or farsightedness. This condition is caused by a shallow eyeball. People with farsightedness can see distant objects clearly, but near objects look blurry.

- Myopia or nearsightedness. This condition is caused by a deep eyeball. People with nearsightedness can see near objects clearly, but not those far away.
- Presbyopia occurs when the lens of the eye loses it elasticity and it can no longer change shape. The condition is usually associated with age and usually becomes evident after age 40. Presbyopia causes people to be somewhat farsighted. Sometimes this is corrected by wearing bifocals (eyeglasses that have a second lens below the top lens). A person with presbyopia can look through the bottom lens while reading and use the top lens for distant objects.
- Astigmatism is blurry vision caused by irregular curves in the cornea (the transparent covering of the eye). The irregular curvature makes it impossible for light rays to focus on a single point.

The First Eyeglasses

An Italian physicist named Salvino degli Armati probably invented eyeglasses in around 1285. He shared the design of his new device with an Italian monk, Allesandro della Spina, who made public the invention and is often given credit for inventing eyeglasses.

In the 14th century, Venetian craftsmen known for their work in glass were making "disks for the eyes." The finely ground glass disks were given the name lenses by the Italians because of their similarity in shape to lentil beans. For hundreds of years thereafter, lenses were called glass lentils. The earliest lenses were convex (they bulged outward in the middle and aided people who were far-sighted). Wearing spectacles become common. By the fifteenth century, eyeglasses had found their way to China.



Most people learn that they need glasses after having an eye exam. Modern opthalmology equipment has made diagnosing possible vision problems much faster and easier.

In 1451 Nicholas of Cusa (1401-1464) in Germany invented eyeglasses to correct nearsightedness using concave lenses. Rather than bulging in the middle like convex lenses, concave lenses are thinner at the center and thicker at the ends.

Eyeglass frames

Early eyeglasses had glass lenses mounted on heavy frames of wood, lead or copper. Natural materials of leather, bone and horn were later used. In the early seventeenth century,

lighter frames of steel were developed. Tortoise shell frames came into use in the eighteenth century. In 1746 a French optician named Thomin invented actual eyeglass frames that could be placed over the ears and nose.

Bifocals

In the United States, Benjamin Franklin (1706-1790) designed the first bifocals in 1760. The top lens could be used to see distant objects and the bottom lens could be used for close work. The two lenses were joined in a metal frame. With this design it was no longer necessary to have two pair of glasses to be able to see clearly.

In England in 1827 Sir George Biddle Airy (1801-1892), an English astronomer and mathematician, made the first glasses to correct astigmatism. To correct this, the exact area of the irregularity of the cornea must first be located. A corresponding area on the eyeglass lens is ground to bring light rays passing through that area into proper focus.

Today eyeglasses come in a wide array of styles and designs. Frames are generally made of metal or plastic, and lenses are made of glass or plastic. In 1955 the first unbreakable lenses were made and in 1971 a new lens came out which combined the properties of plastic with glass. During the 1950s the Varilux was invented. This is a corrective lens of variable strength that can be used in place of bifocals.

[*See also* **Contact lens**]

False teeth

Replacements for decayed or lost teeth have been produced for a few thousand years. The Etruscans (people from the ancient country of Etruria in western Italy) made skillfully designed false teeth out of ivory and bone. These false teeth were secured in the mouth by gold bridgework as early as 700 B.C. Unfortunately, the skills and artistry that went into these efforts were lost until the 1800s.

The Etruscans made skillfully designed false teeth out of ivory and bone. These false teeth were secured in the mouth by gold bridgework.

During medieval times, the practice of dentistry was largely confined to tooth extraction. Replacement and repair were seldom considered. Gaps between teeth were expected, even among the rich and powerful. Queen Elizabeth I of England (1533-1603) filled the holes in her mouth with cloth to improve her appearance in public.

When hand-carved false teeth were installed, they were tied in place with silk threads. If not enough natural teeth remained to tie the dentures to, anchoring false ones was difficult.

Dentures

People who wore full sets of dentures had to remove them when they wanted to eat. Upper and lower plates fit poorly and were held together with steel springs. Because the sets were not anchored, they could spring suddenly out of the wearer's mouth. Even George Washington (1732-1799) suffered terribly from tooth loss and ill-fitting dentures. The major obstacles to progress were finding suitable materials for false teeth, making accurate measurements of a patient's mouth, and getting the teeth to stay in place. These problems began to be solved during the 1700s.

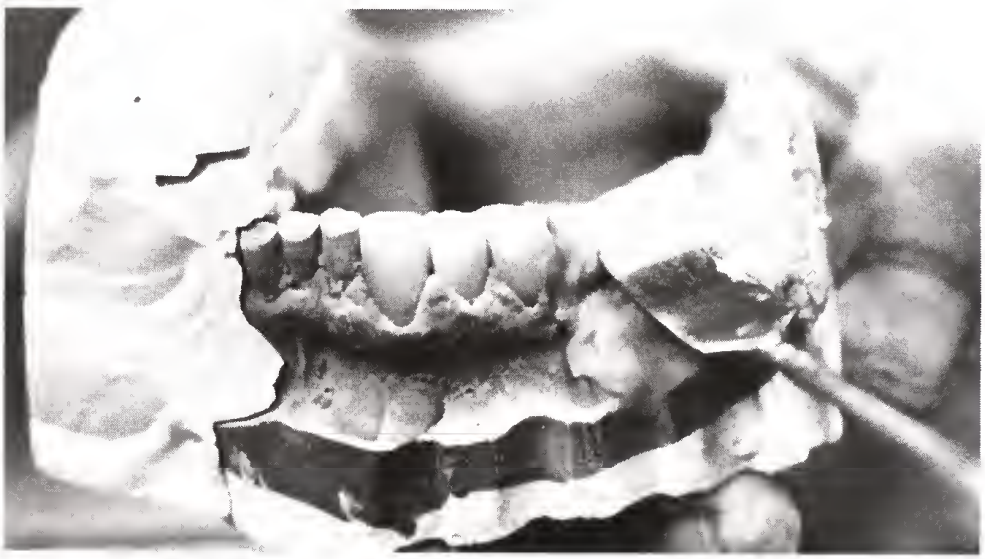
Porcelain

Since antiquity, the most common material for false teeth was animal bone or ivory, especially from elephants or hippopotami. Human teeth were also used, pulled from the dead or sold by poor people from their own mouths. These kinds of false teeth soon rotted, turning brown and rancid. Rich people preferred teeth of silver, gold, mother of pearl, or agate.

In 1774 the French pharmacist Duchateau enlisted the help of the prominent dentist Dubois de Chemant to design hard-baked, rot-proof porcelain (a hard, white ceramic) dentures. De Chemant patented his improved version of these "Mineral Paste Teeth" in 1789 and took them with him when he emigrated to England shortly afterward. The single porcelain tooth held in place by an imbedded platinum pin was invented in 1808 by the Italian dentist Giuseppangelo Fonzi. Inspired by his dislike of handling dead people's teeth, Claudius Ash of London, England, invented an improved porcelain tooth around 1837.

Porcelain teeth came to the United States in 1817 via the French dentist A. A. Planteau. The famous American artist Charles Peale (1741-1847) began baking mineral teeth in Philadelphia, Pennsylvania, in 1822. Commercial manufacture of porcelain teeth in the United States was begun, also in Philadelphia, around 1825 by Samuel Stockton. In 1844 Stockton's nephew founded the S. S. White Company, which greatly improved the design of artificial teeth and marketed them on a large scale.

Porcelain is no longer used because better materials have been developed. Today, dentures are made from either plastic or ceramic. These materials can be tinted to match existing teeth and look more like real teeth than ever before.



Dentures are prepared in a mold. Today, dentures are made from either plastic or ceramic.

Improvements in Fit and Comfort

In 1756 Philip Pfaff (1715-1767) of Germany introduced plaster of paris impressions of patients' teeth. This made it possible to produce dentures that perfectly fit. The real breakthrough in dentures came with the American inventor Charles Goodyear's (1800 - 1860) discovery of vulcanized rubber in 1839. This cheap, easy-to-work material could be molded to fit the mouth and made a good base to hold false teeth. Well-mounted, properly sized dentures could now be made inexpensively.

The timing was ideal. Horace Wells (1815-1848) had just introduced painless tooth extraction using **nitrous oxide.** The number of people having teeth removed skyrocketed. This created a great demand for good, affordable dentures, which Goodyear's invention made possible.

Finsen light

The finsen light is named for its inventor, Niels Tyberg Finsen (1860-1903). It was a powerful light used to cure people of the skin disorder lupus.

Ultraviolet Light (UV)

Finsen received his medical degree in 1891. Over time, he became very interested in how light affects disease. Finsen was familiar with the work of a Swedish researcher who in 1889 had discovered the effects of **ultraviolet light.** The researcher had found that short-wave ultraviolet (the range of radiation wavelengths just outside the color violet in the visible spectrum) light irritated biological tissue more than the longer-waved infrared light.

With this information at hand, Finsen began recording the effects of sunlight on insects and amphibians. He was convinced that light could be used to treat human disease. Finsen found that ultraviolet light from the sun or from electric lights could kill bacteria. He wrote several papers in 1893 and 1894 on the beneficial use of phototherapy.

In 1895 Finsen made an arrangement with Copenhagen Electric Light Works to treat patients two hours each day with ultraviolet light. His patients were diagnosed with lupus vulgaris. This is a skin disease caused by the tubercle bacillus (tuberculosis). Finsen designed a powerful lamp (the finsen light) for the treatment. It was a bright artificial light generated by electrical carbon arcs.

Phototherapy

In 1896 Finsen founded the Finsen Institute for Phototherapy in Copenhagen. The Institute was dedicated to studying effects of light and curing people of disease. At the Institute, 800 lupus patients were treated. Half were cured of the disease and nearly all the rest showed improvement in their conditions. For this achievement Finsen was awarded the 1903 Nobel Prize in medicine. Finsen donated half the prize money to the Finsen Institute.

During Finsen's era both **X-rays** and gamma rays were discovered by the German physicist Wilhelm Röntgen (1845-1923) and the French physicist Antoine-Henri Becquerel (1852-1908). With Finsen's success in light therapy leading the way, the idea of **radiotherapy** was born. Since Finsen's time, X-rays and gamma rays have been frequently used for the diagnoses and treatment of disease.

Even today some foods are irradiated with ultraviolet light to kill bacteria. Finsen was also ahead of his time in his concept of the effect of sunlight on disposition and health. It is only fairly recently that Seasonal Affective Disorder (SAD) has been recognized as a type of depression caused by a lack of sunlight in winter. People diagnosed with SAD can be treated by sitting under lights to extend their exposure to light on short days.

Fleming, Sir Alexander

Alexander Fleming (1881-1955) was one of three men who discovered and developed the first **antibiotic, penicillin.** Fleming was born on a farm in Scotland and worked in a shipping company as a youth. He hated the work, however, and when he received a small inheritance from a relative, he used it to go to medical school. Initially he worked for Almroth Wright, who believed strongly in the effectiveness of vaccinations to prevent disease. But Fleming thought there might be other ways to treat infections.

During World War I (1914-1918), Fleming was further inspired by the problems of wounded soldiers. Immunizations did nothing to stop the bacterial infections which tended to attack the wound sites. Fleming was determined to find a "magic bullet" substance that could destroy these invading bacteria. In 1922, he discovered that the body actually has **enzymes** in tears and mucus (slimy secretions) that, though weak, can kill certain bacteria very quickly.

In 1928 Fleming was still working on the properties of various bacteria when a little bit of luck led to his most important discovery. Fleming had left some microbes (bacteria samples) in dishes in his lab; he had also left the window open. Mold spores from outside landed in the dish and miraculously dissolved the bacteria. Fleming identified the mold as "Penicillium notatum," and he named the substance that actually killed the bacteria "penicillin." While Fleming proved that penicillin was not poisonous to animals, he did not have the means to actually synthesize (artificially create) a pure form of it to use in experiments. The practical purification of penicillin was the later achievement of **Howard Walter Florey** (1898-1968) and **Ernst Boris Chain** (1906-1979). Fleming, Florey, and Chain shared the 1945 Nobel Prize in medicine for their combined research with penicillin.

After receiving the Nobel Prize, Fleming spent the rest of his career doing research at the Wright-Fleming Institute. Because of Fleming's momentous discovery, many previously incurable diseases are now easily treated, and the average human life span has been significantly increased.

Florey, Sir Howard Walter

Howard Walter Florey (1898-1968) was one of two men who developed **penicillin,** the first **antibiotic.** Florey was born in Australia and attended the University of Adelaide before winning a Rhodes Scholarship to study

Florey (second from right) shared the 1945 Nobel Prize in medicine with Alexander Fleming and Ernst Boris Chain.

at Oxford University in England. In the 1920s and 1930s Florey's original research was in inflammatory reactions (such as allergic reactions) where the body produces mucus (a slimy secretion) to expel an irritating invader.

Working With Chain

In 1938, Florey began his work on antibacterial substances. He had hired **Ernst Boris Chain** (1906-1979) to work with him on these problems. Chain brought to Florey's attention **Sir Alexander Fleming** (1881-1955)'s writings on how molds (the origin of penicillin) had killed bacteria in one of his sample dishes. Florey and Chain then worked on synthesizing (artificially creating) a pure form of penicillin. The two researchers tested their conclusions on animals and humans with outstanding results.

After sharing the 1945 Nobel Prize in medicine with Chain and Fleming, Florey traveled to the United States to encourage production of penicillin for routine medical use. As a professor of pathology at Oxford, he also contributed to research on electron microscopy and circulatory and pulmonary (lung and breathing-related) illnesses.

Tooth decay. Most dental professionals believe that flouride helps guard against decay and its complications.

Fluoride treatment, dental

Fluoride is a chemical found in many substances. In the human body, fluoride acts to prevent tooth decay by strengthening tooth enamel and inhibiting the growth of plaque-forming bacteria. After researchers discovered this characteristic of fluoride, fluoridation began. Fluoridation is the process of adding the fluoride to public water supplies.

McKay's Discovery

It all started in the early 1900s with Colorado dentist Frederick S. McKay. McKay noticed that many of his patients had brown stains, called "mottled enamel," on their teeth. McKay set out to find the cause with the help of Greene V. Black (1836-1915) of Northwestern University in Chicago, Illinois. By 1916, McKay

and his team believed the mottling was caused by something in the patients' drinking water.

In 1931 McKay found what he was looking for. He discovered that people who drank water containing a high level of naturally-occurring fluoride had a high degree of tooth mottling. By the early 1940s the United States Public Health Service had already studies the connection between mottling and fluoride and established that one part per million was the ideal level of fluoride in drinking water. This amount substantially reducing decay but did not cause mottling.

Adding Fluoride

Following safety tests on animals, the Public Health Service conducted field tests. In 1945 the public water systems of Newburgh, New York, and Grand Rapids, Michigan, became the first ever to be artificially fluoridated with sodium fluoride. Simultaneously, a group of Wisconsin dentists led by John G. Frisch inaugurated fluoridation in their state.

Results of these tests seemed to show that fluoridation reduced dental cavities by as much as two thirds. Based on those results, the United States Public Health Service recommended in 1950 that all United States communities with public water systems fluoridate. Later that year the American Dental Association (ADA) followed suit, and the American Medical Association added its endorsement in 1951.

Controversy

Even though virtually the entire dental, medical, and public health establishment favored fluoridation, the recommendation was immediately controversial, and has remained so. Opponents objected to fluoridation because of possible health risks since fluoride is toxic (poisonous) in large amounts. Concerns were also raised about citizens being deprived of the choice whether or not to consume a chemical. Because of the controversy, only about 60 percent of the people in the United States now drink fluoridated water. Fluoridation is also practiced in about thirty other countries.

Even though most toothpastes contain flouride, it is still important to get a professional flouride dental cleaning twice a year.

Fluoride and Toothpaste

The initial claims that fluoridation of drinking water produced two-thirds less tooth

decay have been modified to about 20 to 25 percent. In recent years, other ways of applying fluoride have been developed. In the 1950s the Procter & Gamble Company had the idea of adding the chemical to **toothpaste.** In 1956 the company launched a major advertising campaign with their Crest brand of toothpaste. Four years later the Council on Dental Therapeutics of the ADA gave Crest its seal of approval as "an effective decay-preventive dentifrice." The ADA now estimates that brushing with fluoride-containing toothpaste reduces tooth decay by as much as 20 or 30 percent.

Fluoride can also be taken in tablet form, and as a solution either "painted" directly onto the teeth or swished around as a mouthwash.

[*See also* **Toothbrush and toothpaste**]

Folic acid

Folic acid is a member of the vitamin B family. It plays an important role in the synthesis of the amino acids and of components of the nucleic acids. These are essential elements of all cells.

The blood's red and white cells are very sensitive to a folic acid deficiency. Blood disorders are therefore an early sign that the vitamin may be lacking. Megaloblastic anemia and sprue are two such disorders. In the 1930s and 1940s this fact helped attract attention to the newly discovered substance. Folic acid not only reversed certain anemias, but also acted as a growth factor in animals.

Folic acid received its official name in 1941. It was Henry K. Mitchell and two associates who noted that the major source of the compound was green leafy vegetables. They therefore named it for folium, the Latin word for leaf.

In 1945, Robert Angier (1917–) and his coworkers at Lederle Laboratories identified the structure of folic acid and synthesized it.

Fractures, treatments and devices

Fractures, or broken bones, have always occurred. Prompt treatment is important if a patient is to regain full use of an injured arm or leg. In treating a fracture, the bone ends must first be brought back into alignment. After that, the bones must be held together until their ends grow back

together. Closed or simple fractures, in which the bone ends do not penetrate the skin, have always been relatively easy to treat. Open or compound fractures were serious accidents prior to the advent of antiseptics in the 1860s, because infection would set in.

Immobilizing the Bones

The earliest method of holding the bones in place was to use a splint. Splints are strips of stiff material laid parallel to each other alongside the bone. Ancient Egyptians used wood splints made of bark and cushioned with linen. Ancient Hindus treated fractures with bamboo splints. But the splint alone cannot do the job—there must be something to hold the splint in place (a bandage, tape or other wrap).

Casts Replace Splints

Around 1852 Dutch army surgeon Antonius Mathijsen revived the ancient Arabian system and introduced roller **bandages.** The bandages were filled and covered with quick-drying plaster of paris (gypsum) and combined the features of a splint and bandage. Broken bones were held in place while the wet bandages were applied. When the bandages dried, they became rigid. They held the bones perfectly in place during healing. Plaster of paris casts remained standard treatment for fractures until the early 1980s. At that time, casts made of fiberglass plaster came into use. Fiberglass casts are favored for their light weight and water resistance.

Prompt treatment of fractures is important if a patient is to regain full use of an injured arm or leg.

Traction

Fractures have been treated with extension and traction to align the ends of the broken bones from ancient times. The ancient Greeks used traction (pulling on a broken limb with weights and pulleys), but that practice died out until after the Middle Ages. Traction was revived by French surgeon Guy de Chauliac (1300-1368) during the fourteenth century. The English orthopedist Hugh Owen Thomas (1833-1891) devised improved methods of traction.

Screws and Plates

Hugh Arbuthnot Lane (1856-1943) of Great Britain devised a way to hold broken bone ends together mechanically when they would not heal naturally. In 1893 he introduced the use

of steel screws to rejoin bones, then improved the technique around 1905 by using steel plates screwed into the bone ends. These techniques are still in use today but with improved materials for the plates and screws.

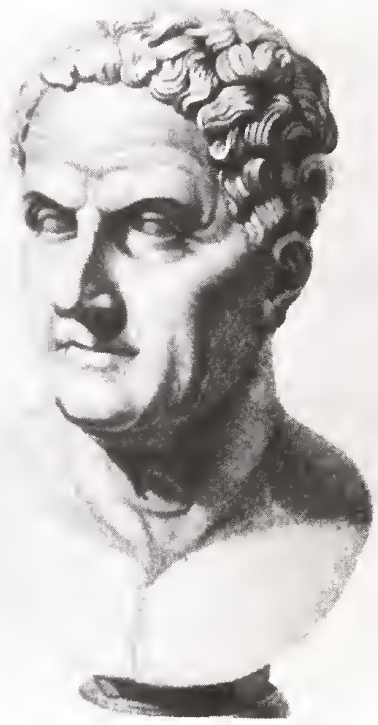
Antiseptics and Compound Fractures

Lane's method of repairing severe fractures could only succeed after the English surgeon **Joseph Lister** (1827-1912) introduced antiseptics to surgery. Compound fractures meant heavy contamination of the wound, which almost always led to severe infection. Because the infection could not be controlled, it usually led to death. Since infection could not be avoided in pre-antiseptic days, the usual method of treating compound fractures was **amputation.** The era of antiseptic surgery began in 1865. It was only then that infection in compound fractures could be controlled.

[*See also* **Antisepsis; Bandages and dressings**]

Galen

Galen (circa A.D. 130-200), the last and most influential of the great ancient medical practitioners, was born in Pergamum in Asia Minor. His father, the architect Nicon, is supposed to have prepared Galen for a career in medicine following instructions given to him in a dream by the god of medicine, Asclepius. Accordingly, Galen studied philosophy, mathematics, and logic in his youth, then began his medical training at age 16 at the medical school of Pergamum attached to the local shrine of Asclepius.



Galen.

At age 20, Galen embarked on extensive travels, broadening his medical knowledge with studies at Smyrna, Corinth, and Alexandria. At Alexandria, the most celebrated research and teaching center of the time, Galen was able to study skeletons, but not actual bodies. This was because religious restrictions forbade the dissection (cutting up) of human remains.

Returning to Pergamum at age 28, Galen became physician to the gladiators, which gave him great opportunities to observe human anatomy and physiology. In A.D. 161, Galen moved to Rome and established a successful practice. He also conducted public lectures and demonstrations, began writing some of his major works on anatomy and physiology, and frequently engaged in vigorous debates with fellow

physicians. In A.D. 174, Galen was summoned to treat Roman ruler Marcus Aurelius; as a result, he later became the emperor's personal physician.

Galen returned to Pergamum in A.D. 166, perhaps to escape a quarrel with his colleagues or to avoid an outbreak of plague in Rome. After a few years, he was summoned back to Rome by Marcus Aurelius. Galen became physician to two later emperors and seems to have stayed in Rome for the rest of his career, probably dying there in about A.D. 199.

Galen was an astonishingly prolific writer, producing hundreds of works, of which about 120 have survived. His most important contributions were in anatomy. Galen expertly dissected and accurately observed all kinds of animals, sometimes mistakingly applying what he saw to the human body. His descriptions of bones and muscle were notable. He was the first to observe that muscles work in contracting pairs, and described the heart valves and the structural differences between arteries and veins. He used experiments to demonstrate paralysis resulting from spinal cord injuries, and the passage of urine from kidneys to bladder. Galen pioneered diagnostic use of the pulse rate. In his extensive travels Galen also collected plants with healing properties and explained their uses.

Galen's Errors

Unfortunately for medieval medicine, Galen made critical errors about the heart and blood vessels that remained virtually unchallenged for 1,400 years. He correctly recognized that blood passes from the right to the left side of the heart, for example, but decided this was accomplished through tiny pores (holes) in the septum (wall separating the two chambers of the heart), rather than through the pumping action of the heart. Galen also believed that blood formed in the liver and was circulated from there throughout the body in the veins. He showed that arteries contain blood, but thought they also contained and distributed pneuma, a vital spirit. In a related idea, Galen believed that the brain generated and transmitted another vital spirit through the (hollow) nerves to the muscles, allowing movement and sensation.

After Galen, experimental physiology and anatomical research stopped for many centuries. Galen's teachings became the ultimate medical authority, approved by the Christian church because of Galen's belief in a divine purpose for all things. The medical world moved on from Galenism only with the appearance of **Andreas Vesalius**'(1514-1564) work on anatomy in 1543 and **William Harvey**'s (1578-1657) studies of blood circulation in 1628.

Gamete intrafallopian transfer (GIFT)

A gamete is a mature male or female reproductive cell. At the time of sex cell formation, the two factors that exist for each heredity characteristic separate equally into two gametes. Each gamete then contains a single heredity factor for each characteristic. The gametes exist within the ovum (egg) and the sperm.

For reproduction to occur, the female ovum (egg) must be fertilized by the male sperm. When the sperm and ovum are brought together by means of a medical procedure, the ovum that is used is not fully developed. It is called an oocyte.

Gamete intrafallopian transfer is a variation of **in vitro fertilization** (IVF). In IVF, oocytes and sperm are gathered and united in a petri (lab) dish. It is in this piece of laboratory glassware that fertilization takes place. In GIFT, oocytes and sperm are gathered and initially prepared as in IVF. However, instead of being united in a petri dish, they are placed in the fallopian tube (one of two ducts that connect the uterus to the area of each of the ovaries) of the foster mother where fertilization will occur.

Gene

The gene is the physical unit of heredity. For each physical trait—such as eye color, height, hair color—a person inherits two genes or two groups of genes, one from each parent. One gene, called the dominant gene, usually overpowers the weaker, called the recessive gene.

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Genes on the same chromosome are called linked genes because they are usually inherited together, such as the genes for hair and skin color. Genes on the X and Y chromosomes are called sex-linked genes, because the X and Y chromosomes are the ones that determine sex. (Men have an XY pair of chromosomes; females have an XX pair.)

Sometimes genes on the same chromosome are not inherited together. When reproductive cells divide to form an egg or sperm cell (a process called meiosis), each chromosome pairs off with a partner. As the chromosomes lie side by side, groups of genes from one chromosome may trade places with groups of genes from the partner chromosome. This is called crossing over and explains how families inherit different combinations of linked traits.

Mendel's Contributions

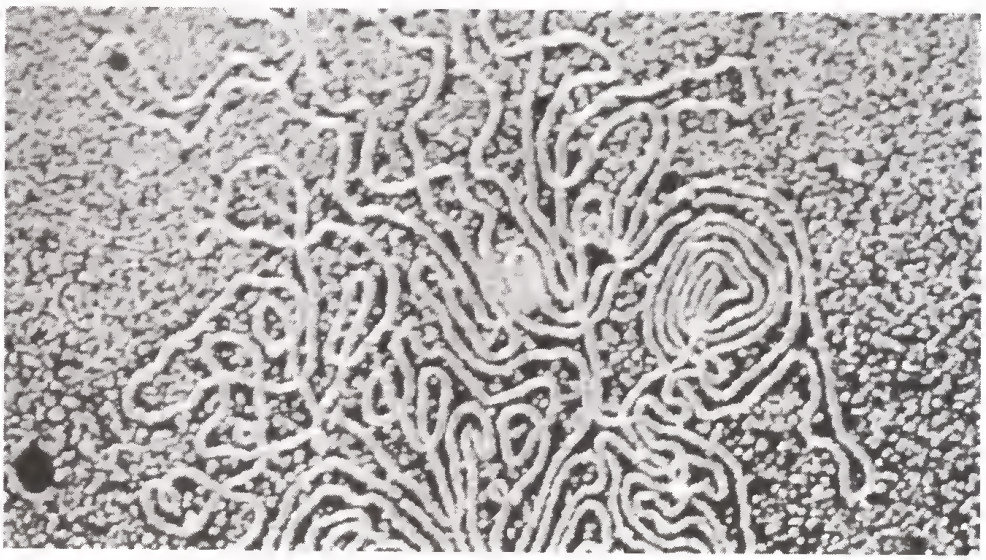
Heredity first began to be understood due to the work of Austrian monk and botanist Gregor Mendel (1822-1884), who discovered that hereditary factors determine all hereditary traits. Although Mendel was not recognized for his work at the time, modern genetic science is solidly based on Mendel's findings.

Experimenting with pea plants, Mendel noticed that the plants inherited traits in a predictable way. It was as though the pea plants had a pair of factors responsible for each trait. Even though he never actually saw them, Mendel was convinced that tiny independent units determined how an individual would develop. Until then, traits were thought to be passed on through a mixing of the mother and father's characteristics, much like a blending of two liquids.

Mendel's laws of heredity were rediscovered in 1900, when they became vitally important to biologists. Among other things, Mendel's laws established heredity as a combining of independent units, not a blending of two liquids. Danish geneticist Wilhelm Johannsen (1857-1927), a strong supporter of Mendel's theories, coined the term "gene" to replace the variety of terms used to describe hereditary factors. His definition of the gene led him to distinguish between genotype (an organism's genetic makeup) and phenotype (an organism's appearance).

Morgan's Genetic Discoveries

The early 1900s brought other advances in the field, including those of the American zoologist Thomas Hunt Morgan (1866-1945), who discovered that genes are located on chromosomes, that genes are linked, and



A gene. Genes are passed from parent to offspring at the time the child is conceived and are located in the chromosomes in the cells of the human body.

Watson and Crick Break the DNA Code

Researchers knew that chromosomes contained deoxyribonucleic (pronounced "dee-oxy-rye-boe-noo-clay-ic") acid, or DNA, which is a subfamily of the nucleic acids. As more experiments showed the connection between DNA and genetics, researchers wondered how a DNA molecule could code for genetic information.

Two scientists, American **James Dewey Watson** (1928-) and Englishman **Francis Harry Compton Crick** (1916-), believed that the structure of DNA held the key to understanding how genetic information is stored in a cell and how it is transmitted from one cell to its offspring. The two researchers used **X-ray crystallography** to "photograph" DNA. On March 7, 1953, Watson and Dewey built a model consisting of two helices (corkscrew-like spirals), wrapped around each other.

Watson and Crick immediately saw how the molecule could "carry" genetic information. The sequence (series) of four nitrogen bases—adenine, guanine, thymine, and cytosine, or A, G, T, C—acts as a **genetic code,** instructing the cell to make specific proteins. The scientists helped decipher the genetic code, a process that involved dozens of researchers over the next decade.

that they cross over. For his research, Morgan received the Nobel Prize for medicine in 1933.

Gene therapy

Gene therapy is a new field in which normal genes are given to patients to cure genetic disorders. Some successes have occurred, as well as some failures. But researchers believe that gene therapy shows promise, because this approach to disease treats the root of the disease instead of just its symptoms.

Three Types of Therapy

Three types of therapy currently exist. In gene replacement therapy, a mutant gene is replaced with a normal gene. In gene augmentation ther-

apy, a normal gene is added but the mutant gene is not removed. And in gene inactivation therapy, a gene is added that will cancel the effects of the defective gene. Sometimes combined to produce the desired cure, the type or types of therapy selected depend on many factors, including whether the actual genetic defect can be pinpointed exactly.

Body Must Be Tricked to Accept Cloned Genes

The point of gene therapy is twofold. First, the gene must be cloned (created), or engineered. This process is also known as recombinant DNA technology (first performed in 1972). Secondly, the normal gene must be introduced into the patient's chromosomes. The body, hoever, actually regards the cloned "normal" gene as foreign, so the it must be tricked into accepting the cure.

Of the various methods tried, the most efficient technique uses an RNA virus called a retrovirus. The retrovirus infects the patient's cells, then copies its DNA into the patient's DNA.

The first human gene therapy was approved for clinical trial in the United States in May 1989. At the end of 1992, at least 37 gene therapy projects were completed, in progress, or approved in China, France, Italy, the Netherlands, and the United States. Each country has its own approval process, designed to protect the patient, the health workers, and the public. By mid-1995 the National Institutes of Health (NIH) and Pharmaceutical Research and Manufacturers of America reported increased efforts in this field. U.S. companies had 57 projects underway, 12 projects completed, and 18 pending, while drug companies had 17 therapies in development.

In the United States, each procedure must be approved by the director of the NIH, by the NIH Recombinant DNA Advisory Committee, and by the U.S. Food and Drug Administration (FDA).

Therapy Trials

Gene therapy trials have included severe combined immunodeficiency (SCID) and malignant melanoma. SCID is a rare disease that prevents the person's immune system from functioning. This well-publicized study concerned the teenager named David who lived for several years in a plastic bubble to protect him from infection.

Some cases of SCID result from ADA deficiency, a genetic mutation that prevents lymphocytes from producing the **enzyme** adenosine deaminase (ADA). Lymphocytes are white, or nearly colorless, cells in the blood and lymph systems produced either by the bone marrow (B cells)

or by the thymus (T cells). T cell lymphocytes are the major players in the body's immune system, which does not develop normally without the enzyme ADA.

In September 1990 NIH researchers R. Michael Blaese and W. French Anderson performed the world's first gene therapy on a four-year-old child with SCID. A normal gene for ADA was inserted into a virus and allowed to "infect" lymphocytes that had been withdrawn from the child's body. Then the girl was injected with the altered cells. During the next 18 months, the patient had several series of injections, along with other treatment. A second patient, a nine-year-old girl, had similar treatments. The cells encouraged production of ADA in both children, who attended school, had only the normal number of infections, and reportedly experienced no side effects. Since then similar treatments have been used on children in other countries.

Many gene therapy studies have been completed or are underway for various cancers. In a study of the skin cancer melanoma, doctors withdrew a sample of the patient's own cells, inserted an altered gene, and returned the new cells to the patient. The purpose of this procedure is to introduce a protein that will kill the melanoma tumor.

Cystic Fibrosis Study Yields Few Results

A gene therapy study for the lung disease cystic fibrosis began in 1992. The therapy calls for inserting a needed gene into an engineered cold virus (the virus is altered so that it will not cause a cold), which the patients inhale. The gene enters the lung and improves cell function, preventing the production of the mucus (a slimy secretion) that blocks a patient's breathing.

The genes performed precisely under laboratory conditions, but in human studies, less than one percent of patients achieved the desired results. The results are not considered to be sufficient enough to be promising.

Further Research

Another study concerned familial hypercholesterolemia, a condition in which patients lack a gene for disposing of harmful low-density lipoprotein cholesterol (the so-called "bad" cholesterol). These patients develop a build-up of this low-density cholesterol in their bodies. People lacking both copies of the gene usually die from a heart attack in their early teens. Someone with only one copy suffers from severe coronary (heart) disease. Scientists at several medical centers are studying insertion of the needed gene into cells from a patient's liver, then injecting the cells into the person's body.

Scientists in China are studying the bleeding disease hemophilia B, which occurs in people whose blood lacks clotting Factor IX. Researchers are attempting to engineer cells with this factor. Studies are also underway on gene therapy for AIDS, liver failure, leukemia, brain tumor, various cancers, rheumatoid arthritis, Gaucher's disease (a metabolic disorder), and various other inherited diseases.

[*See also* **Cloning; Enzyme; Gene; Genetic Engineering**]

Genetic code

The genetic code, which carries the instructions on what a human (or any other living creature) will be like, from color of eyes to tendencies toward disease, is located in specific molecules called nucleotides inside the nucleus (center) of body cells. The genetic material, which is made up of acids in combination with sugar and phosphate molecules is called DNA (deoxyribonucleic acid).

In addition, RNA (ribonucleic acid), a simpler molecule, works closely with DNA by carrying its instructions to the parts of the cell where proteins are made. DNA is structured as a double helix, with two twisted strands parallel to each other with rungs like a ladder between the strands. Each strand consists of four chemical bases—guanine (G), adenine (A), thymine (T) and cytosine (C), while the "rungs" of the ladder are made up of sugar and phosphate.

These bases are repeated in particular arrays of sequences throughout the DNA molecule. The patterns they create provide the instructions on how cells will create proteins and what their tasks will be. DNA is packed into structures called chromosomes within the cell.

History

The discovery of the location of our genetic code began with agriculture. In the 1860s an Austrian monk, Gregor Mendel (1822-1884), showed through his pea breeding experiments that certain characteristics were passed from one pea generation to the next. But he did not know where the pea's genetic instructions were. In 1909 Russian-American chemist Phoebus Theodore Levene discovered DNA and RNA under the microscope, but could not determine their structure.

By the early 1950s, thanks to British chemist **Francis Crick** (1916-) and American biologist **James Watson** (1928-) and their discovery of the

structure of DNA, scientists knew that **genes** were made of this nucleic acid and that specific cell proteins were the products of specific genes. The exact link between DNA and proteins was less well understood, however. Since proteins are considered the language of life, researchers believed that the DNA molecule might be the code for this language. This is how the term "genetic code" originated.

By the 1960s researchers had figured out the relationship between DNA and the cell proteins it gives instructions to, and the long process of finding the codes for specific traits was begun. Once a specific gene can be isolated, its code can then be copied and used to create synthetic genes, which can then be used to change the genetic structures in the human body. In this way, diseases that are caused by defective genes can be cured. Aside from these genetic engineering applications, Watson and his research lab at Cold Spring Harbor are currently working on mapping the entire genetic code (millions of different sequences) for the human body.

We still have a very long way to go in understanding the specific genetic codes for the millions of different traits that make up the human body, but the possibilities for the medical community alone are almost endless.

[*See also* **Genetic engineering**]

Genetic engineering

Genetic engineering is the human altering of the genetic material of living cells to make them capable of producing new substances or performing new functions. The technique became possible during the 1950s when **Francis Crick** (1916-) and **James Watson** (1928-) discovered the structure of DNA molecules. Crick, Watson and later researchers learned how these molecules store and transmit genetic information.

DNA (deoxyribonucleic acid) is found in the nucleus of all living cells. It is structured as a double helix, with two twisted strands parallel to each other with rungs like a ladder between the strands. Each strand consists of four chemical bases: guanine (G), adenine (A), thymine (T) and cytosine (C). These bases are repeated in particular arrays of sequences throughout the DNA molecule. The patterns they create provide the instructions on how cells will develop and what their tasks will be. DNA is packed into structures called chromosomes within the cell.

Gene Splicing

Genetic engineering allows scientists to identify specific genes, remove them, and clone (duplicate) them and use them in another part of the same organism, or in an entirely different one. For instance, cells of bacteria colonies can be changed by genetic engineering to produce proteins, **hormones** or other substances that may be useful in treating illnesses in humans or other animals.

Genetic engineering allows scientists to identify specific genes, remove them, and clone (duplicate) them and use them in another part of the same organism, or in an entirely different one.

This process is called gene splicing or recombinant (as in recombining) DNA technique. Genetic engineers can also increase the amount of certain antibodies for treatment by using hybridomas (altered rapidly growing cancer cells and cells that make antibodies) to form monoclonal antibodies. They can also use the polymerase chain reaction technique to make perfect copies of DNA fragments from very small samples so that the origin of the substance (hair, blood) can be identified. This procedure is used in DNA fingerprinting in criminal cases.

Cloning and Engineering

Although the structure of DNA was discovered in the 1950s, it was not until the early 1970s that scientists figured out how to clone and engineer genes. The first experiments were done with simple organisms such as bacteria, viruses and plasmids (rings of free DNA in bacteria). Hamilton O. Smith, Daniel Nathans and Werner Arber were the first researchers to realize that the bacteria made **enzymes,** called restriction enzymes, that would "cut" DNA chains in specific places. The scientists could then use these enzymes to cut the DNA into segments, cut out a segment that gave disease-causing instructions, and replace it with a segment that gave correct instructions for healthy functioning.

One could also use this technique to alter a bacterium to perform a certain function (such as making **insulin** for sugar metabolism) and then reproduce itself many times to provide this hormones for treating diseases such as diabetes. There are limits to this ability, however. Scientists must start with a complete organism, and cannot change everything in it. They can only make a limited number of changes, so the organism can remain essentially the same. Our knowledge of the total **genetic code** for humans, which contains millions of patterns is limited, so we cannot transfer complicated traits like intelligence, which are a mixture of genetic and environmental influences.

Human Applications

One of the most exciting potential applications of genetic engineering involves the treatment of genetic disorders. Medical scientists now

know of about 3,000 disorders that arise because of errors in an individual's DNA. Conditions such as sickle-cell anemia, Tay-Sachs disease, Duchenne muscular dystrophy, Huntington's chorea, cystic fibrosis, and Lesch-Nyhan syndrome are the result of the loss, mistaken insertion, or change of a single nitrogen base in a DNA molecule.

Genetic engineering makes it possible for scientists to provide individuals who lack a certain gene with correct copies of that gene. For instance, in 1990 a girl with a disease caused by a defect in a single gene was treated in the following fashion. Some of her blood was taken, and the missing gene was copied and inserted into her own white blood cells, then the blood was returned to her body. If—and when—that correct gene begins to function, the genetic disorder may be cured. This type of procedure is known as human **gene therapy** (HGT).

Agricultural Applications

Genetic engineering also promises a revolution in agriculture. It is now possible to produce plants that will survive freezing temperatures, take longer to ripen, convert atmospheric nitrogen to a form they can use, manufacture their own resistance to pests, and so on. By 1988 scientists had tested more than two dozen kinds of plants engineered to have special properties such as these. Domestic animals have been genetically "engineered" in an inexact way through breeding programs to create more meaty animals, etc., but with genetic engineering, these desirable traits could be guaranteed for each new generation of animal.

Plants are genetically engineered in a laboratory beaker. Genetic engineering promises a revolution in agriculture.

Controversy

The potential commercial value of genetically-engineered products was not lost on entrepreneurs (business starters) in the 1970s. A few individuals believed that recombinant DNA would transform American technology as computers had in the 1950s. In many cases, the founders of the first genetic engineering firms were scientists themselves. They were profiting from research that was originally paid for in large part with government funds.

Controversy

As a result, some have questioned whether individual scientists have the right to make a per-

sonal profit from these techniques. As of the early 1990s, working relationships had, in many cases, been formalized among universities, individual researchers, and the corporations they established. But not everyone is satisfied that the ethical issues involved in such arrangements are settled.

Many critics also worry about where genetic engineering might lead. If we can cure genetic disorders, can we also design individuals who are taller, more intelligent, or better looking? Is that a good application of the technology? Will the altered agricultural products be safe for humans, or will they change us in some unknown way? Will the altered bacteria used to create synthetic versions of substances such as insulin create new bacteria that are harmful to humans? Will humans know when to say "enough" to the changes that can be made? These are some of the ethical questions that surround genetic engineering.

Many other applications of genetic engineering have already been developed or are likely to be realized in the future. In every case, however, the glowing promises of each new technique are balanced by the new social, economic, and ethical questions that are being raised.

Genetic fingerprinting

Fingerprints are unique to each individual. Methods of recording and matching fingerprints have allowed police to correctly identify many criminals. Genetic scientists have recently developed another tool for identification based on the uniqueness of each person's **genes.**

Genetic differences between people account for the large variations we see among individuals. Each human has approximately 100,000 genes in the chemical form of DNA. No two humans, except for identical twins, have exactly the same **genetic code.** A description of a person's DNA that is detailed enough to distinguish it from another person's DNA is called a DNA or genetic "fingerprint."

History

In 1984 English researcher Alec Jeffreys developed a technique to display a person's genetic code as an **X-ray** picture of bands of dark and light. These bands were the result of attachment of radioactive segments of DNA to certain sites on the DNA fragments, creating a unique pattern for the individual. This direct DNA analysis revealed so much variation in the genetic

code between different people that even a small section of the entire genetic code could identify an individual's special combination of traits.

Erlich's Method

Three years later, Henry Erlich developed a method of DNA fingerprinting so sensitive that it could be used to identify an individual from an extremely small sample of hair, blood, semen, or skin. Erlich's technique used Jeffreys' traditional method and combined it with a new technique called polymerase chain reaction (PCR).

Using his new method, Erlich was able to duplicate and heat-separate the DNA fragments from a single human hair root many times. The amplified DNA was then used to obtain a DNA fingerprint.

Applications

Genetic fingerprinting has already proved to be a very useful tool. Initially, it was used exclusively in forensic (criminal) science and law. This technique has helped to link suspects to crimes where a single drop of blood was the only clue. When there is a need to know who an individual's biological mother or father is, genetic fingerprinting can provide the answer by matching DNA elements between parent and child.

DNA fingerprinting must be done with great care, however, since any contamination of blood samples by mixing them or touching them with ungloved hands, etc., can produce false results, with serious consequences in legal proceedings, such as a trial. If carefully done, however, genetic fingerprinting can provide accurate identification of an individual.

Genetically engineered blood-clotting factor

Factor VIII

Excessive, uncontrolled bleeding can be fatal. Hemophilia is the most common chronic condition that involves uncontrolled bleeding. Hemophiliacs lack a protein called factor VIII, which is required for blood to clot normally. Although purified factor VIII extracted from human blood became available around 1960, it has been very expensive. In addition, impurities in the human factor VIII placed many hemophiliac patients at risk of contracting serious diseases, including hepatitis and, later, AIDS.

Genetically engineered blood-clotting factor

Artificially Created Factor VIII

In the early 1980s, scientists at Genentech, Incorporated, and Chiron Corporation in California and at the Massachusetts-based Genetics Institute began developing genetic engineering techniques to obtain pure, inexpensive factor VIII artificially. **Genetic engineering** refers to methods of rearranging **genes**—removing or adding them or transferring them from one organism to another.

At Genentech, Richard Lawn, Gordon Vehar, and their coworkers succeeded in isolating the normal gene for factor VIII in healthy people and inserting it into hamster cells, where it joined with the genetic material of the hamsters. The hamster cells then used the new genetic instructions to make pure human factor VIII.

A major problem with this promising method of treating hemophilia inexpensively and safely is that it is difficult to control the amount of factor VIII that the cells produce, and too much factor VIII causes the blood to stop circulating properly. The researchers are continuing their tests to develop a proper dosage of Factor VIII for hemophiliacs, thus making their treatment safer and much more reasonable in cost.

Haller, (Victor) Albrecht von

Albrecht von Haller (1708-1777) was one of the great heroic figures of early biology. He is considered the father of neurology, the study of the nervous system. Born in Bern, Switzerland, Haller was not a healthy child, but he displayed great intellectual talents at an early age. He wrote scholarly articles at the age of eight and by the age of ten had completed a Greek dictionary. Haller enrolled as a medical student at the University of Leyden and earned his degree at the age of 19. Haller began his own medical practice in 1729 at the age of 21, and continued in private practice until 1736. He was then appointed Professor of Anatomy, Botany, and Medicine at the newly created University of Göttingen.

Haller Studies Nerves and Muscles

Haller had interests and talents in a wide range of fields, but he is probably best known for his work on nerves and muscles. When he began his research, little was known about the structure and function of nerves or about their control of muscles. A popular theory of the time held that nerves were hollow tubes through which a spirit or fluid flowed. Haller rejected this idea, however, since no one had ever been able to locate or identify such a spirit or fluid.

Instead, Haller concentrated on two specific reactions that seemed to involve the nerves: irritability and sensibility. By irritability Haller meant the contraction of a muscle that occurs when a stimulus is applied to the muscle, such as when one feels pain from a hot object, and the muscles move one's arm, leg, etc., away from the heat. Haller found that irritability increases when the stimulus is applied to the nerve connected to a mus-

cle, so he concluded that the stimulus was transmitted from the nerve to the muscle.

In his study of sensibility, testing to see which body tissues could "feel," Haller found that ordinary tissue does not respond to stimuli, but that nerves do. He showed that stimuli applied to nerve endings traveled through the body, into the spinal column, and eventually into the brain. By removing certain parts of the brain, he was then able to show how each part affects specific muscular actions.

Haller continued his research at Göttingen until 1753, when he returned to Bern. He spent the remaining twenty years of his life in research, writing, and government service until he died in Bern on December 17, 1777.

Hallucinogens

Hallucinogens are natural and synthetic (synthesized) substances that, when ingested (taken into the body), significantly alter one's state of consciousness. Hallucinogenic compounds often cause people to see (or think they see) random colors, patterns, events, and objects that do not exist. People sometimes have a a different perception of time and space, hold imaginary conversations, believe they hear music and experience smells, tastes, and other sensations that are not real.

Hallucinogen Classification

Many types of substances are classified as hallucinogens, solely because of their capacity to produce such hallucinations. These substances are sometimes called "pyschedelic," or "mind-expanding" drugs. They are generally illegal to use in the United States, but are sometimes sold on the street by drug dealers. A few hallucinogens have been used in medicine to treat certain disorders, but they must be given under controlled circumstances. Hallucinogens found in plants and mushrooms were used by humans for many centuries in spiritual practice worldwide.

Unlike such drugs as **barbiturates** and amphetamines (which depress or speed up the central nervous system, respectively) hallucinogens are not physically addictive (habit-forming). People can become psychologically dependent upon them, however. The real danger of hallucinogens is not their toxicity (poison level), but their unpredictability. People have had such varied reactions to these substances, especially to LSD (lysergic acid diethylamide), that it is virtually impossible to predict the effect a hallucinogen will

have on any given individual. Effects depend upon the person's mood, surroundings, personality, and expectations when taking the drug.

Hallucinogens and Spirituality

Some users of hallucinogens have reported feeling mystical and insightful, while others are fearful, paranoid (excessively suspicious or mistrustful of others), and hysterical (exhibiting overwhelming or unmanageable fear or emotional excitability). Medicine men, shamans, and other spiritual leaders have used natural hallucinogens found in plants and mushrooms since ancient times, believing in their power to help contact the spiritual world or mystical beings for guidance in serving their people.

Pollen from flowers and other plants—most with medicinal properties—was found in the grave of a Neanderthal man in Shanidar, Iraq. Scientists believe that since these prehistoric people very likely knew how to use plants for medicine, they probably used hallucinogenic plants in rituals. Archaeological evidence also shows that psychoactive drugs (drugs that affect the mind or behavior) were used in ancient Egypt, Greece, Europe, and many other cultures.

Natural hallucinogens are formed in dozens of psychoactive plants, including the peyote cactus, various species of mushrooms, and the bark and seeds of several trees and plants. In Mexico, mushrooms called Psylocybe mexicana, which contain the fungi psilocybin and psilocin, have been used in religious rituals since the time of the Aztec civilization (before 1519, an empire in Central America noted for its advanced social development). In Europe, the fungus Amanita muscaria was thought to have been used by the Vikings. Amanita muscaria and its close relative, Amanita pantherina, are also found in the United States. Both contain psychoactive ingredients called ibotenic acid and muscimol.

Some members of the Native American Church, an organization made up of Native Americans from tribes throughout North America, practice the use of mescaline, a form of psychedelic drug found in the peyote cactus. Currently peyote is the only psychedelic agent that has been authorized by the federal government for limited use during Native American religious ceremonies.

LSD crystals. Hallucinogens have been studied for possible medical uses, including the treatment of some forms of mental illness, alcholism, and addiction to the drug opium.

A few less common natural hallucinogens are also used in religious practice. These include ololiuqui (morning glory) seeds, which are eaten by Central and South American Indians both as intoxicants (a substance, such as alcohol, that excites or makes one insensible) and hallucinogens. Harmine, another psychedelic chemical that has been used for centuries, is obtained from the seeds of Peganum harmala, a plant found in the Middle East. The feeling of exhilaration (cheerfulness, excitement) brought about by this drug is sometimes followed by nausea, fatigue, and sleep. People using the drug may experience visual distortions (for instance, an object appears to be in a different shape from what it really is) like those induced by LSD.

DMT (dimethyltryptamine)is a hallucinogen found in the seeds of certain West Indian and South American plants. People in Haiti have used this drug, in the form of a snuff (a tobacco product inhaled through the nostrils, chewed, or placed against the gums) called cohoba, in religious ceremonies.

Marijuana, LSD, and PCP

Marijuana and hashish, two substances derived from the hemp plant (Cannabis sativa), are also considered natural hallucinogens, although their potency (power) is very low when compared to others. Marijuana (also called grass, pot, tea, weed, or reefer), a green herb from the flower of the hemp plant, is considered a mild hallucinogen. Hashish is marijuana in a more potent, concentrated form. Both drugs are usually smoked. Their effects include a feeling of relaxation, faster heart rate, the sensation that time is passing more slowly, and a greater sense of hearing, taste, touch, and smell.

Even the most potent of these naturally occurring hallucinogens is not nearly as powerful and unpredictable as the synthetic hallucinogen LSD, which is chemically derived from ergot, a parasitic fungus (a fungus that lives in or on a host, deriving benefits from the host while injuring it) that grows on rye and other grains. LSD became well known in the 1960s, when many people sought spiritual enlightenment through the use of drugs.

A form of LSD was first produced in 1938, when Albert Hoffman, a Swiss research chemist at Sandoz Laboratories, synthesized many important ergot alkaloids (organic plant bases), including Hydergine, LSD-25, and psilocybin. Hoffman accidentally experienced the first "LSD high" when a drop of the material entered his bloodstream through the skin of his fingertip. Hoffman could hardly recount his experience after it was over. He was the first to record LSD's ability to cause the user to experience synesthesia, an overflow of one sensory ability into another. For example, a person experiencing synesthesia may hear colors and see sounds.

The physical effects of hallucinogens are considered small compared to their effects on the mind. Death from an overdose of hallucinogens is highly unlikely, but deaths have resulted from accidents or suicides involving people under the influence of LSD. The drug made them so indifferent to the world around them they thought they could step out of a window, for example, without harm. LSD is sold on the street in various forms, sometimes on a piece of paper marked into squares, with each square being one dose.

LSD is so powerful that a tiny amount can have a hallucinogenic effect. Just three pounds of LSD could cause a reaction in all the people in New York City and London combined. Because it is so strong and its action so unpredictable, LSD is considered very dangerous.

The drug phencyclidine, or PCP, known as "angel dust" and "rocket fuel," was widely abused in the late 1970s. PCP is dangerous because it produces a sense of indifference about the world and a reduced sensitivity to pain. Combined with hallucinogenic effects, it can result in bizarre thinking and violently destructive behavior.

Taking hallucinogens can cause sweating, excessive salivation, decreased heart rate, increased blood pressure, and change in pupil size. LSD users may experience flashbacks of visions they had when on the drug. Some LSD users suffer organic brain damage, which results in impaired memory and attention span, confusion, and difficulty in thinking. Some scientists believe hallucinogens affect serotonin, a neurotransmitter (a substance that transmits nerve impulses) in the brain. Recently several hallucinogenic compounds have been found to resemble serotonin structurally. One theory is that at least some drug-induced hallucinations are due to changes in the functioning of serotonin neurons. It was demonstrated that LSD interfered with the transmitter action of serotonin.

Medical Uses of Hallucinogens

Hallucinogens have been studied for possible medical uses, including the treatment of some forms of mental illness, alcholism, and addiction to the drug **opium.** They have also been given to dying patients. Most of these uses have been abandoned, however.

A synthetic form of the active chemical in marijuana, THC, has been approved for prescription use by cancer patients who suffer from severe nausea after receiving **chemotherapy**(treating cancer with drugs). THC is also used to reduce eye pressure in treating severe cases of glaucoma. PCP is occasionally used by veterinarians as an anesthetic and sedative for animals.

Harvey, William

William Harvey (1578-1657), the father of modern physiology, was the first researcher to discovery the circulation of blood through the body. Although we take this knowledge for granted, until Harvey's time, people were not aware that the blood travels through the body and is pumped through its course by the heart.

Harvey was born in England in 1578, the eldest of seven sons of a farmer. While five of the other Harvey brothers became London merchants, William studied arts and medicine at Cambridge University, where he received a bachelor of arts degree in 1597. He then earned his medical degree in 1602 from the famous medical school at Padua, Italy. Returning to London, Harvey began what became a very successful medical practice while also working in medical research.

In 1609 Harvey was appointed to the staff of St. Bartholomew's Hospital. He was elected a fellow of the Royal College of Physicians in 1607. Harvey's ideas about circulation of the blood were first publicly expressed in lectures he gave in 1616. Harvey became court physician to King James I (ruled England from 1603-1625) in 1618 and then to Charles I (ruled England from 1625-1649) in 1625, a post he held until Charles was beheaded in 1649. Charles provided Harvey with deer from the royal parks for his medical research, and Harvey remained loyal to Charles even during the Cromwellian Civil War (1642-1660), in which the Parliamentarians who fought against the King ransacked Harvey's rooms and destroyed many of his medical notes and papers. Harvey retired at the end of the Civil War a widower. He lived with his various brothers and died of a stroke in 1657.

William Harvey.

Harvey's Contribution

Harvey's great contribution to medicine was his revolutionary discovery of the circulation of blood. By dissecting both living and dead animals, Harvey became convinced that the ancient Greek anatomist **Galen**'s ideas about blood movement must be wrong, particularly the ideas that blood was formed in the liver and absorbed by the body, and that blood flowed through the septum (dividing wall) of the heart. Harvey first studied the heartbeat, establishing the existence of the pulmonary (heart-lung-

heart) circulation process and noting the one-way flow of blood. When he also realized how much blood was pumped by the heart, he realized there must be a constant amount of blood flowing through the arteries and returning through the veins of the heart, a continuing circular flow.

Harvey Publishes His Findings

Harvey published this radical new concept of blood circulation in 1628. It provoked immediate controversy and hostility from the medical community of the time, contradicting as it did the usually unquestioned teachings of Galen. The most virulent critic, Jean Riolan, scorned Harvey as a "circulator," an insulting term for a traveling quack. Harvey calmly and quietly defended his work, and although his medical practice suffered for a time, his ideas become widely accepted by the time of his death. The discovery of capillaries by Marcello Malpighi in 1661 provided factual evidence to confirm Harvey's theory of blood circulation.

In addition to his blood circulation research, Harvey was one of the first to study embryology (the study of reproduction in its earliest stages) by observing the development of the chick in the egg. He performed many dissections of mammal embryos at various stages of formation. From these experiments Harvey was able to formulate the first new theory of animal generation since antiquity, emphasizing the primacy of the egg, even in mammals. Prior to Harvey's work, it was thought that the male sperm was the primary source of new life, and that the egg was simply an empty home, so to speak, for the sperm to develop.

Thanks to Harvey's willingness to abandon old wisdom and observe and test for himself, we have our modern understanding of physiology.

Hearing Aids and Implants

Hearing aids are electronic devices that amplify sound for people with impaired (damaged) hearing. Millions of hearing aids are sold annually. Hearing aids are similar to a public address system, but in miniature. They consist of a microphone, amplifier, receiver, and battery.

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Two Types of Devices

Two types of hearing aids are available: those that conduct sound through the air and those that conduct sound through bone. Most people who are hearing impaired can use an air-conduction hearing aid. This type amplifies sound and transports it directly into the ear via a small tube.

For people who have a problem hearing sound waves transmitted through the inner or middle ear, however, the bone-conduction hearing aid is recommended. This type of hearing aid uses a small vibrator clamped to the bony part of the head behind the ear. The bone transmits the sound waves to the nerves of the ear.

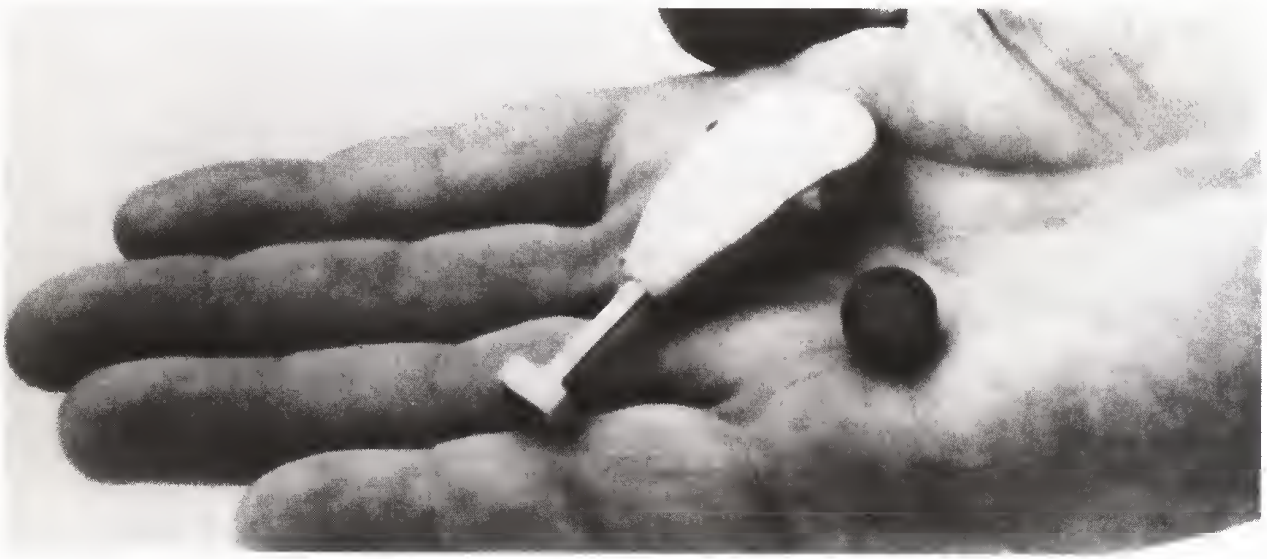
A Typical Hearing Aid

A typical hearing aid contains a microphone, which picks up sounds and converts them into electric signals. The hearing aid's amplifier increases the strength of the electric signals, and then the receiver converts the signals back into sound waves that can be heard by the wearer. The entire mechanism is housed in an earmold that fits snugly in the ear canal. A small battery provides the power to run the electronic parts.

Hearing aids are manufactured in a variety of designs to fit the need of the wearer. Some are small enough to be completely concealed by the ear canal, yet powerful enough to adjust to the desired level of amplification.

Hearing Aids in History

Devices to aid hearing have a long history. The idea of bone conduction was known in the early seventeenth century, and the ear trumpet was used even before that time. The ear trumpet was shaped to gather sound and funnel it into the ear. In seventeenth-century Germany, Marcus Banzer used a piece of swine bladder connected to a tube made of elk hoof to make an artificial ear drum. Later in that century the audiphone, or



At the time of its release in 1987, this hearing aid developed by Bristol-Meyers was considered revolutionary due to a unique design.

dentiphone, was invented. Made of a flexible material such as cardboard, the device was shaped like a fan and held at its end between the teeth as the fan was bent toward the sound. The sound vibrations captured by the fan were carried to the teeth, the bones of the jaw and skull, and finally to the auditory nerve, where sound could be heard.

Perhaps the largest hearing aid ever made was an imposing throne built for King John VI of Portugal in 1819. The hollow carved arms of the chair terminated with the wooden mouths of lions through which people would speak and have their voices carried by tubes to the king's ear.

Yet another artificial ear drum was devised in 1852 when the English physician Joseph Toynbee used a disk of vulcanized rubber attached to a rod. The Victorian era was known for some of its more elaborately concealed hearing devices, hidden in urns, top hats, even tiaras.

In the 1870s, Alexander Graham Bell (1847-1922) began experimenting with the conduction of sound through electrical devices, originally intending to help deaf children hear. His experiments led to the invention of the telephone instead, but his work did bring public awareness to the needs of the hearing impaired. Miller Reese Hutchinson invented the first electrical hearing aid in 1901, and he called it the Telephone-Transmitter.

The era of vacuum tubes like those used in early radio saw the inroduction of new types of hearing aids, starting in 1920 with Earl Charles Hanson's Vactuphone. A 1923 model produced by the Marconi Company was the Otophone, consisting of an amplifier placed in a large case weighing 16 pounds (7 kg), making it rather bulky to use. A. Edwin Steven invented the first "wearable" hearing aid, weighing 2.5 pounds (1.1 kg), in 1935. During the 1950s, transistors revolutionized electronics, and Microtone introduced its compact and powerful transistor hearing aid in 1953.

Implants

People who are profoundly hearing impaired and cannot successfully use a hearing aid sometimes can have an implant to improve hearing. The first cochlear implants were done in 1973. In this procedure, an electric device that stimulates the remaining functional nerves in the inner ear are implanted into people with nerve deafness. Although the implant does not restore normal hearing, it does help the recipient hear and interpret environmental sound. Today, more sophisticated multichannel electrical cochlear implants that contain speech processors allow some patients to understand speech without reading lips.

Robert V. Shannon of the House Ear Institute of Los Angeles has developed an auditory brainstem implant for people in which the auditory nerve has been severed. The implant consists of a tiny microphone, a sound processor, and a transmitter that are all outside the ear and an electrode that is implanted inside the head, connected to the auditory brain stem. When the microphone picks up sound, the unit converts sound energy into electric signals that are sent directly to the brain, where they are interpreted as sound. Although the implant is not enough to restore hearing, it upgrades the level of environmental sound heard by the user, and at least one implant volunteer has been able to understand limited human speech.

Heart-Lung Machine

One of the major milestones in medicine was the development of artificial circulation, also known as heart-lung bypass. Before the heart-lung machine was invented, heart surgeons operated blindly, with the heart still pumping, or by slowly chilling the patient's body until circulation nearly stopped, or by connecting the patient's circulatory system to a second person's system during the operation. All of these methods were extremely risky.

Gibbon's Research

An American surgeon named John H. Gibbon Jr. (1903-1974), began pursuing the goal of total artificial circulation in 1931 after a young female patient died of blocked lung circulation. Gibbon realized that it was necessary to keep oxygenated blood circulating without use of the heart, especially to the brain, to carry out careful operations on the heart under direct vision. His pursuit was to last for almost three decades.

After years of intensive experiment, John Gibbon, his wife, Mary, and others were able to construct a heart-lung machine to allow such artificial circulation. On May 6, 1953, surgery using the heart-lung machine was successfully performed on the first human, 18-year-old Cecilia Bavolek, to close a hole between her upper heart chambers. Gibbon's original heart-lung machine was massive, complicated, and difficult to manage. It damaged blood elements and caused bleeding problems and severe consumption of red blood cells. Because of its ability to permit corrective operations to be performed inside the human heart for the first time, however, these drawbacks of heart-lung bypass were considered acceptable. The era of **open heart surgery** had begun.

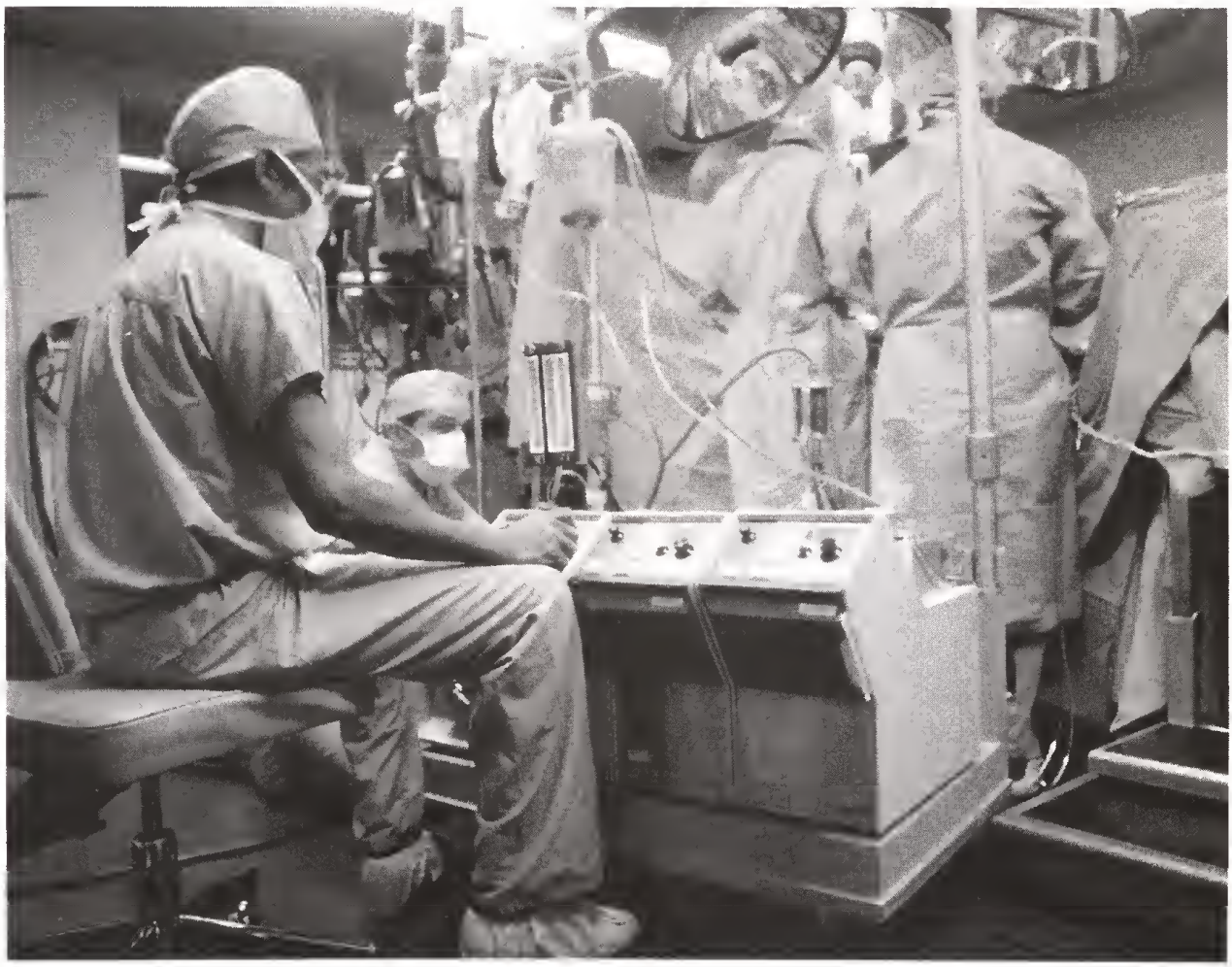
Product Improvements

Gradually, the safety and ease of use of heart-lung equipment improved. With today's state-of-the-art machines, minimal blood trauma occurs during heart-lung procedures. It is now commonplace for surgeons to stop the heart from beating for several hours while the circulation is maintained by heart-lung equipment.

Now that patients can be kept alive during heart surgery, a whole new range of operations has become possible. Congenital heart defects (those occurring at birth) can be repaired. Diseased or damaged heart valves can be replaced. Coronary bypass surgery, in which a replacement blood vessel is used to carry blood flow around a blocked section of artery, is commonplace. Thanks to Gibbon's heart-lung machine, open-heart surgery, especially coronary bypass, has become routine throughout the world.

How It Works

Blue blood withdrawn from the upper chambers of the heart is



A heart-lung machine. Before the heart-lung machine was invented, heart surgeons operated blindly with the heart still pumping.

siphoned into a reservoir. It is then pumped through an artificial lung to expose it to oxygen. When the blood is passing through the lung (or oxygenator), it comes into close contact with the surfaces of the machine itself. Oxygen gas is delivered to the interface between the blood and the machine, allowing the blood cells to absorb oxygen molecules directly. The blood is now red in color, owing to its rich content of oxygen. The heart-lung machine next pumps the red blood back into the patient through a tube. The heart-lung circuit is a continuous loop: as the red blood goes into the body, blue blood is drained into the pump.

Hippocrates

Hippocrates. His contributions to medicine include detailed observations of disease and its effects, and an understanding of how health is often influenced by external factors

Greek physician Hippocrates of Cos (circa 460-377 B.C.) is often called the "father of medicine". His contributions to medicine include detailed observations of disease and its effects, and an understanding of how health is often influenced by diet, breakdowns in bodily processes, and the environment.

Facts about the life of Hippocrates are rare. Some information, however, is consistent. Hippocrates was born on the island of Cos into a family of doctors. He taught at the widely-regarded medical school on the island and traveled widely throughout ancient Greece and the Mideast giving lectures. Quite famous during his lifetime, Hippocrates died at a fairly old age in Larissa.

In his school, Hippocrates tried to separate medical knowledge from myth and superstition. Modern knowledge about Hippocrates' methods comes from the *Corpus Hippocratum,* a collection of 70 volumes that seems to have been gathered in the great Library of Alexandria around 200 B.C. While few of these books were probably written by Hippocrates himself, they are widely considered to be an expression of his medical teachings and philosophy.

The Hippocratic approach to medicine emphasized diet and the clinical examination of biological functions. In his lectures and teachings, Hippocrates noted that the environment can affect health in both positive and negative ways.

He also advanced the idea of the "four humors," whereby disease was supposed to result from an imbalance in the body's four important fluids.

Hippocrates is credited with writing about preventive medicine. He and his followers were very concerned about preserving health through proper diet and activities, such as exercise and getting enough rest.

Hippocrates was not content to simply work on the causes and treatment of disease. He advised medical practitioners to be serious about their profession and have high moral standards. These standards are embodied in what we call the "Hippocratic Oath," which doctors still swear to today. According the Oath, a physician is required to swear to use his knowledge only to save a life, not to take it; not to cause abortion; to maintain a professional relationship with patients; and not to reveal secrets given to him by patients.

Hopkins, Frederick Gowland

Frederick Gowland Hopkins (1861-1947) is credited with the discovery of **vitamins** and their function in the diet. Thanks to his research, we now understand the importance of these substances in promoting health and preventing disease.

Born in Sussex, England, Hopkins had a lonely and unhappy childhood. He was brought up by his widowed mother and an unmarried uncle who tended to ignore him. When Hopkins was 17, his uncle chose a career in insurance for him and for several years he dutifully gave in to his uncle's wishes. At the same time, however, he also took part-time courses in chemistry at the University of London, eventually getting his degree.

In 1888, already 27 years old, Hopkins received the small inheritance that finally enabled him to enter medical school at Guy's Hospital in London. After getting his doctoral degree in 1894, Hopkins joined the staff of Guy's Hospital and taught for several years. In 1898 he was invited to teach physiology and anatomy at Cambridge University and it was at Cambridge that his long, distinguished career really began.

In 1901, while working with S.W. Cole, a student at Cambridge, Hopkins discovered tryptophan, an important amino acid, and was able to isolate it from protein. A few years later Hopkins demonstrated that tryptophan and certain other amino acids could not be manufactured in the body from other nutrients but had to be supplied the diet. By so doing, he laid

the foundation for the concept of the essential amino acids necessary for proper body functioning.

After his work with tryptophan, Hopkins's primary interest became the study of diet and its effect on metabolism (the physical and chemical processes necessary for maintaining the body). At the time, nutritional science was in a fairly primitive state. Most researchers confidently believed that a well-rounded diet consisted of the proper mixture of fats, proteins, carbohydrates, mineral salts, and water, and that the so-called diet-linked illnesses—such as beriberi or scurvy—were caused by some toxic substance in certain foods.

Studying the literature—including reports by **Christiaan Eijkman** (1858-1930) that polished rice seemed to cause beriberi (a nerve disease), while unpolished rice effected a cure—Hopkins began to have serious doubts about this nutritional theory.

Hopkins had already noticed that his laboratory rats failed to grow on a diet of artificial nutrients, but grew rapidly when he added tiny amounts of cow's milk to their daily rations. He suspected that normal food must contain substances missing from the pure fats, proteins and carbohydrates routinely used in nutritional studies. Hopkins called these substances "accessory food factors" and decided that they were necessary for growth. His two papers on the subject, in 1906 and 1912, are considered the first explanations of the concept of vitamins.

For their pioneering work in vitamin research, Hopkins and Eijkman received the 1929 Nobel Prize in medicine. Hopkins was knighted in 1925 and received numerous other awards in the 1920s and 1930s. He was a great inspiration to all of his students, many of whom became professors. Hopkins died in Cambridge in 1947.

Hormone

Hormones are chemical messengers that regulate bodily processes such as growth, reproduction, metabolism, digestion, mineral and fluid balance, and the functioning of various organs. In animals, hormones are secreted by organs, tissues, and glands of the endocrine system directly into the blood by and carried in the bloodstream to target organs. Once there, they alter the activities of the organ or regulate the production of other hormones.

Hormones aid in determining an animal behavior patterns and also the probability that a particular behavior will occur. Hormones exert substantial control over the following behavior patterns: parental care, terri-

torial behavior, metamorphosis (in insects), foraging behavior, and circadian rhythms (behavior patterns that always occur at the same time each day). Most hormones fall into two main categories: peptides (chains of amino acids) and lipids (which include **steroids**).

The Endocrine System

The endocrine system produces many hormones. The major endocrine glands are the pituitary, located at the base of the brain, the thyroid and the parathyroid in the neck, and the pancreas, adrenals, and gonads (reproductive glands) in the torso. Hormones are also produced by the stomach, the small intestine, and the kidneys.

The Pituitary Gland

The tiny pituitary gland was once considered to be the "master gland" of the body. Today, scientists realize that the hypothalamus modulates the activities of the pituitary. The pituitary gland is composed of two lobes, the anterior pituitary and the posterior pituitary. The anterior pituitary produces six major hormones, and the posterior pituitary stores two hormones originating in the hypothalamus. The pituitary's target endocrine glands are the thyroid, adrenal gland, and the gonads. Through these glands it controls the growth of the skeleton and regulates the functions of the thyroid and the gonads. One pituitary hormone, called growth hormone, must be secreted in just the right amount for normal growth in childhood. If too little is produced, the child will become a dwarf; if too much is secreted, the child will grow to be a giant.

Thyroid Hormones

Thyroid hormones stimulates oxygen consumption and metabolism, regulating the growth of body tissues and the rate at which food is burned to provide body energy. They also increase the sensitivity of some organs, especially the central nervous system. If the thyroid becomes overactive, it produces a condition called hyperthyroidism, which causes nervousness and irritability. Another thyroid condition, cretinism, is caused by a congenital lack of thyroid secretion. It is marked by greatly stunted physical and mental growth.

Insulin and Glucagon

The pancreas produces two important hormones, **insulin** and glucagon. Insulin affects most cells in the body because it is involved in the metabolism of carbohydrates, proteins, and fat. Too little insulin results in diabetes, a condition of high levels of blood sugar resulting in weakness

and dehydration. Too much insulin causes very low levels of blood sugar, resulting in weakness, anxiety, and convulsions. Glucagon raises the blood sugar level. Together, insulin and glucagon help keep a normal level of glucose in the blood.

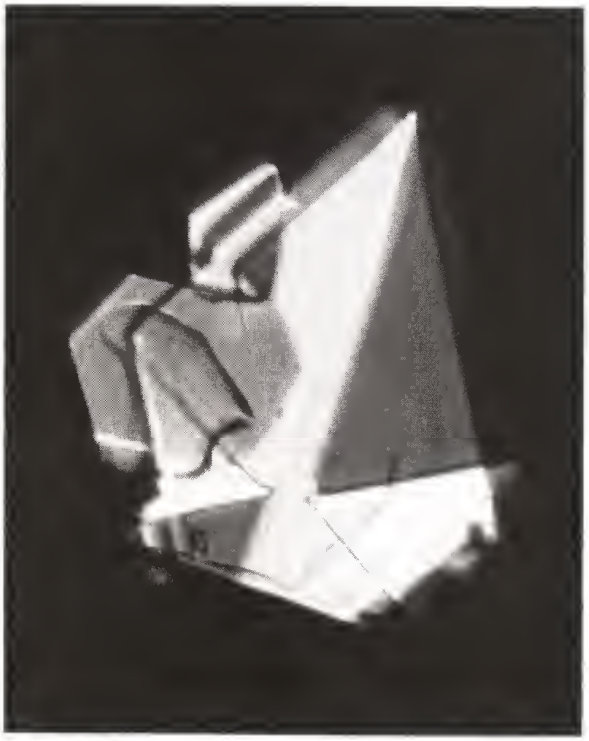
Adrenal Glands and Gonads

Hormones in the adrenal glands control the concentration of salts and water in body fluids and are necessary for maintaining life. They also produce sugar from proteins and store it in the liver to help maintain resistance to physical and emotional stress.

Hormones found in the gonads control sexual development and reproductive processes. A fetus's sex is determined by genetics, but certain hormones produced by the gonads (under the influence of the pituitary gland) must be present for the fetus to develop appropriate sex organs.

Early Discoveries

The term hormone (from the Greek for "to spur on") was first used by the British biochemists William Bayliss and Ernest Starling in 1904. The duo coined the term to describe the action of a digestive substance they had isolated called secretin, which stimulates the flow of pancreatic juice. Scientists later realized that the first hormone to have actually been isolated and synthesized (artificially created) was the adrenal hormone **epinephrine,** identified by Japanese American chemist Jokichi Takemine in 1901.



Beef insulin hormone. Most hormones fall into two main categories called peptides and lipids.

The isolation of the thyroid hormone **thyroxine** in 1914 by American biochemist Edward Kendall marked another important milestone in understanding how hormones work. Too much or too little thyroxine can cause illness. One of the earliest thyroid disorders diagnosed was Graves' disease (a disease of the thyroid gland resulting in increased size and activity of the gland). Its cause is unknown, but it is believed to be an autoimmune disorder, and it occurs most often in women. Graves' disease often results in bulging eyes, tachycardia (fast and irregular heartbeat), and thickening of the skin.

One of the most well known developments in endocrinology was the isolation of insulin by the Canadian physicians Frederick Banting and

Charles Best in 1921. Soon various types of injectable insulin were being used to treat diabetes.

The 1920s also saw the discovery that the pituitary gland stimulates the sex organs and the introduction (in 1928) of the first pregnancy test. Soon after, the relationship between female sex hormones and the menstrual cycle was explained. Working from this relationship, **Gregory Pincus** would introduce the first oral contraceptives in the 1950s.

In the 1920s and 1930s it was also learned that the adrenal glands contain hormones that control the concentration of salts and water in body fluids and are essential for maintaining life. Adrenal hormones are also essential for sugar and protein formation and storage in the liver. They also help resist physical and emotional stresses In the 1930s, Kendall and the Swiss chemist Tadeus Reichstein both isolated one of these hormones, cortisone, which is a **steroid.**

American researcher Philip Hench used **cortisone** to reduce inflammation in rheumatoid arthritis and other connective tissue diseases in the 1940s, making cortisone the first hormone to be used medically.

Synthetic Hormones

Scientists eventually learned to make some hormones in the laboratory. Vincent Du Vigneaud, an American biochemist, synthesized the small pituitary hormone oxytocin, which regulates milk production in the mammary glands and causes uterine contractions. This led to the synthesis of many larger and more complex hormones for medical purposes.

Today, hormone production can be automated, yielding a great deal of synthetic hormone at a rapid rate to meet increasing medical demands. Patients with hormone deficiencies can often be treated effectively with these artificial hormones. Diabetics, for example, receive insulin. Patients suffering from dwarfism are given **human growth hormone.** Oral contraception combines the use of estrogen and progesterone to prevent ovulation and thus pregnancy. Hormones are also used to treat infertility.

Human growth hormone

Human growth hormone (GH), also called somatotropin, is a protein that stimulates growth. GH must be secreted (released) in just the right amount in a child for normal growth to take place. If too litle is human growth hor-

mone is produced, the child will become a dwarf; if too much is secreted, the child will grow to be a giant.

GH is secreted by the anterior pituitary gland, located at the base of the brain. The pituitary has a direct effect on the metabolism of proteins, carbohydrates, and lipids and controls the growth rate of the skeleton and internal organs.

If too litle human growth hormone produced, a child will become a dwarf. If too much is secreted, the child will grow to be a giant.

Gigantism and Acromegaly

The notion of a growth hormone arose from clinical observations on gigantism and acromegaly. Gigantism is a condition caused by too much GH in childhood and marked by much greater height than usual. Acromegaly is caused by too much GH in adulthood and is marked by a thickening of the bones in the feet, hands, and face. In the 1930s, American biologist Herbert Evans (1882-1971) demonstrated how extracts from the pituitary gland can greatly stimulate animal growth, producing gigantism.

In the 1940s, Evans and his colleague Choh Hao Li isolated the growth hormone from cattle. Other scientists isolated growth hormones in different animal species. In 1970, Li and other scientists independently synthesized GH using **genetic engineering** techniques. This led to the first production of genetically engineered human growth hormone in the 1980s by Eli Lilly and Company and Genentech (a bio-research organization).

Lack of normal amounts of GH during childhood can result in a type of dwarfism in which the person is small but has normal proportions and intelligence. Injections of GH can achieve remarkable results and help the person reach normal or near-normal size if the condition is diagnosed while the bones can still grow (before the long bones have closed).

GH Release

The pituitary releases GH when it receives a signal from the brain's hypothalamus in the form of growth hormone releasing hormone (GHRH). Release, however, can also be triggered by stress, exercise, emotional excitement, fasting, sleep, or hypoglycemia (low blood sugar). Release is inhibited by the hormone somatostatin and may be inhibited by lack of sleep, high blood sugar (hyperglycemia), obesity, a high blood level of free fatty acids, and by growth hormone itself. American endocrinologist Roger Guillemin and colleagues isolated somatostatin in 1973 and growth hormone releasing hormone (at that time called growth hormone releasing factor; now known to be a hormone) in 1984.

The pharmaceutical firm of Hoffmann-La Roche announced in 1989 that it had developed an artificially produced growth hormone releasing hormone which, when administered, stimulates the body to produce normal amounts of growth hormone. This may have advantages for a patient because a smaller dose is required than that of growth hormone. Also, GHRH is a much smaller molecule, so it can be administered by a skin patch or inhalant, rather than by injection.

An Ethical Dilemma

Since the introduction of synthetic growth hormone in the late 1980s, a controversy has arisen over efforts to boost the growth rate of children who are on the border between being of regular height and being unusually short. Some children are simply short because their parents are. Many physicians are wary of treating short children who do not have GH deficiency just for cosmetic or social reasons. They believe the children's parents, who are short themselves, are trying to prevent their children from the failures the parents experienced as children and blame on their being short. Also, the long-term effects of such treatments are not known.

On the other side of the issue are parents, as well as some researchers, who claim that short children are socialized according to height rather than chronological age. It is claimed that they are stigmatized by abnormal appearance and have poor academic achievement, low self-esteem, and poor social skills.

Researchers in a 1994 study on the subject, reported in the journal *Pediatrics,* concluded that GH therapy should not be routinely administered to short children to improve their psychological health. The report urged physicians to consider both a child's short stature and psychosocial functioning before making a decision.

[*See also* **Gene; Hormone**]

Hydrogen peroxide

Hydrogen peroxide is a chemical compound of hydrogen and oxygen. (It can be thought of as water with an extra oxygen atom.) Pure anhydrous hydrogen peroxide is a colorless, syrupy liquid that it rapidly decomposes into oxygen and water. Hydrogen peroxide is also a strong disinfectant cleanser and bleach. In nature, hydrogen peroxide is created in the atmosphere when ultraviolet rays strike oxygen in the presence of moisture. Ozone is free oxygen with an extra atom of oxygen. When ozone comes

into contact with water, this extra atom of oxygen splits off easily. Water combines with the extra oxygen atom to become hydrogen peroxide .

Thénard's Studies

Louis Jacques Thénard (1777-1857), a French chemist, is credited with discovering hydrogen peroxide. One of the first things he found out about hydrogen peroxide is that it attacks the skin, producing painful blotches (fortunately, this effect wears off completely within a few hours). Thenard had tried for many months to formulate the chemical. At the time, however, scientists did not know how much oxygen could be combined with water. In 1818 Thénard finally succeeded in preparing pure hydrogen peroxide, which he called "oxygenated water," and determined its density.

In addition to attacking the skin, the chemical also reacts explosively with metal oxides, as Thénard soon discovered. For several years afterward, he continued to study the compound, defining its properties and using it to prepare new peroxides (other compounds containing extra oxygen).

Multiple Uses

One of the first uses of hydrogen peroxide was to restore old paintings by removing sulfur compounds from their surface. Today hydrogen peroxide has found many more valuable applications, mainly in industry but also for medical purposes. Because the chemical is a strong oxidant (it combines with other compounds to produce oxides and water), it is widely used as a commercial bleaching agent in the production of cotton, wool, and delicate fabrics that would be destroyed by other agents. Even though it costs more than chlorine bleach, hydrogen peroxide is preferred in these applications because its action on fibers is milder and it leaves no undesirable residues.

The chemical is also used cosmetically in hair bleach. In concentrated forms, hydrogen peroxide has found high-technology applications as a fuel additive for rockets, sumarines, and jet planes. In the computer industry, hydrogen peroxide has found widespread for washing transistors and integrated chip parts before assembly.

Dental and Medical Applications

Hydogen peroxide has numerous medical applications. It has long been used as an antiseptic to prevent infection and to cleanse and treat mouth sores. Today it is also used as a mouth wash and as a teeth whitener. The demand for whiter, brighter teeth became a booming business in the mid-1990s. More than a dozen products were introduced, all promising to fix yellow, stained teeth. Most of these whiteners rely on chemicals known

as "oxygenating agents" to bleach teeth. The most common ingredient is a ten percent concentration of carbamide peroxide, which in contact with mouth fluids breaks down into hydrogen peroxide. This process also releases a highly reactive form of oxygen. Scientific studies have suggested that in some circumstances oxygenating agents can damage tissues and harm the pulp or interior of the teeth and even cause genetic mutations.

For years hospitals have used high-pressure steam sterilizers. These machines require temperatures too hot for many sensitive insruments. In the 1950s, hospitals began using low-temperature sterilizers, but the process was time-consuming and relied on ethylene oxide, a carcinogenic (cancer-causing) gas. In 1996 a California company, Advanced Sterilization, introduced a new instrument sterilizer for hospitals. The device is a low-temperature sterilizer fueled by a simple household chemical long used to fight infection: hydrogen peroxide.

[*See also* **Gene**]

Ibuprofen

Ibuprofen is a non-steroid drug often used to treat arthritis and relieve pain, fever, and swelling. Its development resulted from a search to find a drug more potent (powerful) and better tolerated than **aspirin.** When ibuprofen was approved for over-the-counter (OTC) use in the United States in May 1984, it was the first new OTC pain relief medication to enter the marketplace in a generation. Prior to ibuprofen's introduction, nonprescription pain relief was mainly provided by aspirin, marketed since 1899, and acetaminophen, introduced in 1955.

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Early Testing

Ibuprofen was developed by Boots Laboratories, a British drug manufacturer and retailer. Early in the 1960s researchers at Boots identified carboxylic acid as the agent that gave aspirin its anti-inflammatory (soothing) property. The Boots group investigated other carboxylic acids. When they found one that was twice as strong as aspirin, they synthesized and tested more than 600 compounds created from these acids. The most active of these, propionic acid, was chosen for clinical trial. It proved to be ineffective in treating rheumatoid arthritis. The researchers next turned to other compounds they had synthesized from phenylalkanoic acids, which seemed to offer broader anti-inflammatory features. The most effective and useful of these was ibuprofen, which Boots began to sell in 1964 in the United Kingdom as the prescription medication Brufen.

Motrin, Advil, and Nuprin

In 1974, ibuprofen first appeared in American pharmacies after Boots

granted a nonexclusive license to the Upjohn Company, which marketed ibuprofen as the prescription arthritis-relief drug Motrin. A few years later, Boots began selling its own prescription-form ibuprofen, called Rufen, in the United States.

When the United States Food and Drug Administration approved OTC sales of ibuprofen at a lower dose than in prescription form, two major drug companies immediately geared up for major production. The Whitehall Laboratories division of American Home Products came out with Advil. This was soon followed by Nuprin, which was produced by Upjohn and marketed by Bristol-Meyers. Both companies operated under licenses from Boots, which held the worldwide patent for ibuprofen until May 1985. The companies also held exclusive marketing rights until September 1986. After that date, new manufacturers jumped into the lucrative market with products of their own, including Johnson & Johnson with Medipren, Thompson with Ibuprin, and a number of other companies with generic and private-label brands.

Ibuprofen, aspirin, and acetaminophen are chemically different from one another, but all three give effective relief for minor aches and pains. Ibuprofen causes fewer stomach problems than aspirin. It is also more effective for many women in relieving menstrual discomfort. It seems to be more effective for postsurgical dental pain and soft-tissue injuries, but cannot be taken by people with certain conditions, such as an allergy to aspirin.

Ibuprofen. Research has revealed that high doses of ibuprofen slow lung disease in patients with cystic fibrosis.

A report in the May 1995 issue of *Medical Sciences Bulletin* detailed a new medical application for ibuprofen. Research has revealed that high doses of ibuprofen slow lung disease in patients with cystic fibrosis. At high doses the drug inhibits release of lysosomal **enzymes** and the migration, adherence, swelling, and aggregation of neutrophils (white blood cells). Researchers believe that ibuprofen may prolong survival among cystic fibrosis patients with mild lung disease.

Incubator

Ancient Designs

An incubator is an enclosed chamber used for maintaining a living organism in a controlled

environment. The ancient Egyptians and Chinese both devised incubators to hatch chicks from eggs without having the mother hen sit on them. This enabled hens to continue laying eggs without interruption. Egyptian incubators were large rooms heated by fires where attendants turned the eggs at regular intervals so they would warm evenly. Chinese incubators were warmed by fire or by rotting manure.

Incubator Enhancements

In 1588 Jean Baptiste Porta, an Italian inventor, drew on the ancient Egyptian design to build an egg incubator. He was forced to abandon his work during the Spanish Inquisition (a 1478 movement instituted by King Ferdinand and Queen Isabella of Spain during which many people were tortured and killed in the name of religion). Later on, Dutch inventor Cornelius Drebbel also invented an incubator to hatch eggs.

Frenchman René-Antoine Ferchault de Réaumur (1683-1757) revived interest in egg incubation in Europe around 1750. Réaumur's device was warmed by a wood stove. The temperature was controlled by a **thermometer** he also invented, which gave rise to the temperature scale named after him. The success of Réaumur's incubator—French king Louis XV (1710-1774) enjoyed helping the chicks hatch—helped boost commercial production of foodstuffs at the beginning of the industrial era.

The incubator was further developed by Abbé Jean-Antoine Nollet (1700-1770) and later by Abbé Copineau, who used alcohol lamps as a source of heat. Modern egg incubators are huge and may handle a million eggs at a time.

Incubator Babies

The 1880s saw the introduction of incubators to keep premature (born too early) or extremely weak babies warm. Often, the incubators were warmed by pans of hot water placed under them. Étiene Stéphane Tarnier, a French obstetrician (1828-1897), devised an incubator for the care of prematurely born infants. It was warmed by a kerosene flame and used at the Paris La Maternité (a birthing hospital). A number of "incubators with living children" were demonstrated in Turin, Italy, at the 1898 Italian Exhibition.

Today incubated infants are enclosed in chamber that is well ventilated (allows for the movement of air), with the temperature maintained at about 31 to 32 Celcius (88 to 90 Fahrenheit). The air is also humidified and filtered. The incubators are made of plastic and Plexiglas. Incubators have contributed to the much-improved infant survival rate, even of very low birth-weight infants.

A baby grows stronger under care in an incubator.

Inoculation

Inoculation is the injection of dead or weakened disease-causing bacteria or viruses into the human body in order to produce immunity against (prevent infection by) that disease. Because the organisms injected into the body are dead or weakened, they can create immunity without causing the disease. The material injected into the body is called a vaccine.

The term vaccination originally referred to immunization against smallpox because the procedure originated when English physician **Edward Jenner** (1749-1823) discovered that milkmaids who had contracted the mild disease cowpox (vaccinia) were immune to smallpox. The development of a cowpox vaccine against smallpox has led to the production of vaccines against a wide range of diseases.

Variolation

Long before the colonial period in Africa, some tribes practiced a method of protection against smallpox called variolation. It involved inserting fluid from smallpox blisters under the skin. This was intended to produce a mild form of the disease and give the person immunity from severe illness. In some parts of Asia, a mixture of smallpox scabs and pus was pricked into the skin. The Chinese blew powdered scabs into the nostrils.

The technique of scratching smallpox fluid onto healthy people was introduced to Britain and western Europe in the early 1700s. Variolation became quite popular for a short time but soon lost favor as its potential dangers became more apparent. The procedure also became popular in the American colonies for awhile, but was eventually outlawed by several states until shortly before the American Revolution (1775-1783). Variolation remained controversial until Jenner's famous 1798 announcement.

Discovery of the Smallpox Vaccine

In eighteenth-century Europe, a smallpox epidemic raged. In the cramped medieval towns, the disease was fueled by garbage and even human excrement (waste) clogging the narrow streets and inadequate sewers. One in ten persons died of the disease, most of them children. It is said that one in three persons in London bore pit marks from smallpox.

Common folk wisdom spread the idea that anyone who contracted cowpox, a similar, milder disease of cows, became immune to human smallpox. In 1796 Jenner decided to test an idea. He took some cowpox fluid from the sores of a milkmaid named Sarah Nelmes and rubbed it into cuts on the arm of an eight-year-old boy named James Phipps. A few days later

James came down with a mild case of vaccinia (a form of cowpox contracted by humans), but soon got over it. Six weeks later, Jenner gave James some fluid from a person who had smallpox. The boy was not affected and had gained immunity from the inoculation. To describe the inoculation, Jenner coined the term vaccine, from the Latin word vaccinus, or "of cows."

Because of the success of his vaccine, Jenner was given a grant of money to continue his work. Soon thousands of English citizens were vaccinated, including the royal family. The practice spread to Germany and Russia. The president of the United States at the time, Thomas Jefferson, wrote to Jenner congratulating him on his success. When Jenner's vaccination was made available in America, Jefferson made sure that members of his family were vaccinated against smallpox. Jefferson praised Jenner for having found a way to rid humanity of smallpox. For half a century smallpox remained the only disease for which there was a vaccine.

Disease Prevention

Attitudes about disease prevention slowly began to change during the 1800s. People began to realize that filthy living conditions, dirty drinking water, and the lack of proper sewer systems could be associated with outbreaks of disease. Pioneers in health care, including nurse Florence Nightingale and surgeon **Joseph Lister,** (1827-1912) brought on the sanitary movement by calling for clean instruments and bedding in hospitals. Increasing numbers of surgeons began using **antiseptic** methods, even though many still did not believe that microorganisms, or germs, caused disease.

A girl gets an inoculation. Inoculation is the injection of dead or weakened disease-causing bacteria or viruses into the human body in order to produce immunity.

Louis Pasteur and Germ Theory

In the mid-nineteenth century, French chemist and microbiologist **Louis Pasteur** (1822-1895) was developing his germ theory. The theory held that specific microorganisms cause specific diseases. Pasteur's first experience with microorganisms as the cause of disease occurred when he was investigating a disease of silkworms in 1865. The disease had almost destroyed the French silk industry. Pasteur was able to prove that the disease was caused by a microorganism. This microorganism infects the moth that lays the eggs from which the silkworms hatch. Weeding out the affected eggs and removing the source of infection saved the silkworm industry.

Even more important, however, was the implication of Pasteur's research. It suggested that relating specific microorganisms to specific diseases might have relevance to the causes of human illness.

Koch's Report

In 1876 **Heinrich Robert Koch** (1843-1910) reported on his work on the fatal illness in sheep called anthrax ("splenic fever"). He gave details of how the anthrax bacillus (a bacterium) could be grown and isolated. He also noted that the bacillus could still produce the disease in animals even after living for several generations in a laboratory. Koch's report aroused Pasteur's interest in the relationship of microorganisms to disease. Pasteur soon had developed a method to protect animals against anthrax by injecting the animals with anthrax bacilli that had been severely weakened by a special treatment; this prevented the bacilli from causing the disease. These findings were reported in 1881 and established the principle that the disease-producing properties of a microorganism can be so weakened that it will produce immunity to the disease without actually producing the disease.

Over the next few years Pasteur applied this new principle to develop a method for preventing rabies in persons bitten by rabid animals. In 1885 a young boy named Joseph Meister who had been bitten by a rabid dog was brought to Pasteur. Because other doctors agreed with Pasteur that the outlook for the boy was hopeless, Pasteur decided to try to inoculate him against the rabies. When the boy failed to develop signs of rabies, Pasteur knew that his theories and experiments had been correct. The success of Pasteur's antirabies vaccine gained him much attention and marked the first time that his methods had been applied directly to humans.

After that breakthrough, bacteriology and immunology proceeded at rapid pace. Pasteur's assistant, Pierre-Paul-Émile Roux (1853-1933), continued their work in bacteriology, concentrating on the disease diph-

theria. He found that not only did a specific bacteria cause diphtheria, but a toxin (poison) produced by the bacteria caused disease symptoms. Together with Alexandre-Émile Yersin (1863-1943), he isolated the diphtheria bacillus and developed an antitoxin to counteract the diphtheria. Soon scientists discovered more and more bacteria, developed numerous vaccines, and learned new techniques to prevent other diseases.

Insulin

Insulin is a hormone produced by the pancreas (a gland that releases a digestive juice into the intestine). The pancreas is composed of acinar cells, which produce digestive enzymes, and the islet cells of Langerhans, which produce **hormones.**

What Insulin Does

Four hormones are produced by the Langerhans islet cells. Insulin is produced in the B cells, glucagon in the A cells, somatostatin in the D cells, and pancreatic polypeptide in the F cells. Insulin promotes anabolism (building up of tissues) and inhibits catabolism (breaking down of tissues) in muscle, liver, and fat cells. It increases the rate of synthesis (blending) of glycogen, fatty acids, and proteins. Lack of insulin causes diabetes mellitus (a disease characterized by excess sugar in the blood and other body fluids).

Insulin's most important feature is its ability to increase the rate of glucose (a crystalline sugar) absorption by cells. Glucose is the most efficient fuel used by and found in almost all cells. Insulin causes a decreased concentration of glucose in the blood and causes the cells to store glycogen (a starchlike substance), mostly in the liver. It also promotes the entry of other sugars and amino acids into the muscle and fat cells. Insulin is therefore responsible for promoting fat storage in fat cells and for the total quantity of protein in the body.

Insulin Production

Insulin production is stimulated by high levels of glucose and inhibited (limited) by lower levels of glucose. Insulin regulates glucose with glucagon. Glucagon catabolizes (changes into a product of simpler composition) glycogen to glucose and also raises the blood sugar. Glucagon can be given to increase the blood sugar when intravenous (by needle) glucose cannot be given. Glucagon takes about twenty minutes to raise the

blood sugar. Intravenous glucose raises it instantaneously, which is why it is preferred in treatment. Together insulin and glucagon ensure that the body stores and maintains the proper level of glucose for its energy needs.

Diabetes

Diabetes is from the Greek word meaning "siphon," and "mellitus" comes from melliferous, meaning "of or relating to honey." Diabetes has been recognized for centuries and was originally diagnosed by tasting the urine and finding it sweet (melliferous). The high sugar also causes the kidneys to excrete (or siphon) large amounts of water. In 1815, French chemist Michel Eugène Chevreul discovered that the sweetness came from grape sugar or glucose. Later discoveries showed how the body makes, stores, and uses glucose.

Injury to the pancreas was linked to diabetes beginning in the seventeenth century and confirmed by animal experiments, particularly those of the German physiologist Joseph von Mehring (1849-1908) and a Russian pathologist, Oscar Minkowski (1858-1931). The acinus cells were found in the seventeenth century by the Dutch anatomist Regnier de Graaf and the islet cells in 1869 by a German pathologist Paul Langerhans (1847-1888).

Hormones

In 1905 English physiologists Ernest Starling and William Bayliss discovered hormones. Hormones are substances secreted (released) by glands and carried in the blood to control cell activity elsewhere. In 1916 an English physiologist named Edward Sharpey-Schäfer proposed that a hormone produced by the pancreas lowered the level of glucose in the blood. He called the hormone "insuline," the Latin word for "island," because he believed it came from the islet cells of the pancreas.

Credit for discovering insulin is given to Canadian surgeon Frederick Grant Banting (1891-1941) and Canadian physiologist Charles Herbert Best (1899-1978). Banting and Scottish physiologist and professor John James Rikard Macleod (1876-1935) were jointly awarded the Nobel Prize for medicine in 1923. Banting gave half of his share to Best, and Macleod gave half of his share to James Bertram Collip, because of the men had contributed to the discovery.

The first drop of biosynthetic insulin. This synthetic product was made by Eli Lilly and Company using recombinant DNA technology

The First Insulin Patient

Collip, a professor at the University of Alberta, had experience in the chemistry of hormones. Prior to January 1922, he had prepared an insulin pure enough to be used on human patients. The first patient to receive insulin was 14-year-old Leonard Thompson. Thompson was admitted to Toronto General Hospital with a high blood glucose level; he also was urinating between three and five liters of fluid per day. Despite his rigid diet of only 450 calories (the only known treatment at this time was a diet low in carbohydrates), Thompson continued to excrete (get rid of through bodily waste) large amounts of glucose. On January 11, 1922, he was given insulin. Within a fairly short time, his blood sugar level came down and he stopped urinating large amounts of liquid.

Humulin

In 1982 insulin became available as a genetically-engineered product called Humulin. Humulin's structure is identical with human insulin. The A and B chains are produced separately in different strains of E. coli bacteria. The E. coli have been genetically encoded to produce each of these strains. The strains are separated from the bacteria and purified. The purified chains are combined chemically and repurified.

Interferon

Interferon is a protein produced by animals in response to viral infections. It is a defensive mechanism by the body to prevent multiplication of the virus. The action of interferon was first demonstrated in 1957 by British virologist Alick Isaacs (1921-1967) and his Swiss colleague Jean Lindenmann. Isaacs was born in Glasgow, Scotland, in 1921, to a Russian Jewish family. He studied medicine at Glasgow University but found he preferred research to the actual practice of medicine.

Viral Interference

Early in his studies of influenza (flu) at the World Influenza Centre at the National Institute for Medical Research in England, Isaacs became interested in the viral interference phenomenon, first described in 1935. It was observed that an RNA virus in a cell inhibits (restrains) the growth of any other viruses in that cell. While trying to discover the mechanism by which this occurs, Isaacs found that the interference seemed to be caused by something inside the cell.

While working with the visiting Swiss scientist Jean Lindenmann in 1957, Isaacs found that chick embryos (developing eggs) injected with influenza virus released very small amounts of a protein that destroyed the virus. The protein also inhibited the growth of any other viruses in the embryos. Isaacs and Lindenmann named the interfering protein interferon.

It is now known that interferon is produced within hours of a viral invasion and that most living things, including plants, can make the protective protein. Interferon was initially seen as the cell's first line of defense against viral infections, and its discovery was expected to pave the way for successful treatment of viral diseases. Researchers soon found, however, that interferon is "species-specific." (Only human interferon, for example, will work in human beings.) The body also produces interferon in only small amounts, making it extremely expensive to obtain. These difficulties caused interferon research to inch forward at only a slow pace.

New Interest

The late 1960s saw renewed interest in interferon when Ion Gresser (1928-), an American researcher in Paris, discovered that the protein stopped or slowed the growth of tumors in mice and also stimulated the production of tumor-killing lymphocytes (white blood cells). Gresser and Finnish virologist Karl Cantell both developed a way to make interferon in useful amounts from human blood cells. Monoclonal antibodies, first produced in 1975, made large-scale purification of interferon possible. The mid-1980s saw the advent of genetically- engineered interferon, the first example of which was produced from bacteria by Swiss scientist Charles Weissmann in 1980.

Research of interferon's ability to kill cancer cells has yielded only mixed results. It has been successfully used, however, against leukemia and osteogenic sarcoma (a bone cancer). Interferon shows varied promise in treating one type of multiple sclerosis, melanoma, renal cell cancer, and a few AIDS-related Kaposi's sarcomas. Interferon is also used to treat viral diseases like rabies, hepatitis, and herpes infections.

[*See also* **Gene**]

In vitro fertilization

In vitro fertilization (IVF) is the term used to describe the combination of egg cells and sperm in a glass petri dish in order to fertilize the eggs. "In vitro" comes from the Latin word meaning "in glass." The procedure is

used to treat infertility, a condition in which, for various reasons, a woman cannot become pregnant.

In the procedure, eggs are removed from the woman's uterus, fertilized with sperm, and then returned to the uterus to produce a pregnancy. The first baby conceived by in vitro fertilization, Louise Brown, was born in England in 1978. Since then, more than 3,000 babies conceived in this way have been born.

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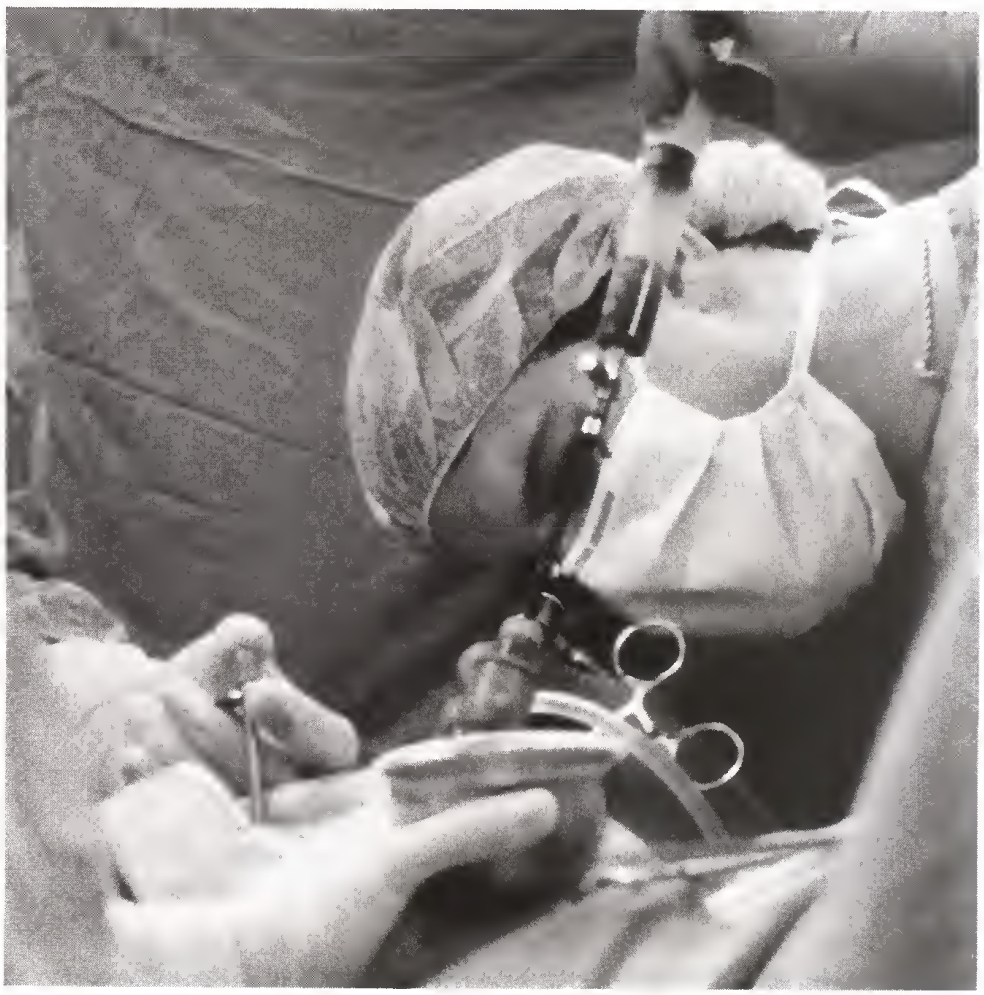
Early Attempts

Early attempts at IVF were made over a century ago, with a successful rabbit embryo transfer carried out by Walter Heape in England. **Gregory Pincus** (1903-1967) performed further IVF experiments in the 1930s. An editorial in the *New England Journal of Medicine* in 1937 suggested IVF as a treatment for infertility in women. Although human IVF experiments were carried out in the 1940s and 1950s by John Rock (1890-) and Landrum



An in vitro fertilization procedure. Although its success rate is considered modest, IVF is a popular infertility treatment.

Variations on IVF

Several variations on IVF are now practiced. One is called gamete intrafallopian transfer (GIFT), in which eggs and sperm are gathered and prepared just as in IVF. Then they are placed into the woman's fallopian tube for fertilzation to occur, rather than in a petri dish. Another method is called zygote intrafallopian transfer (ZIFT), in which one or more zygotes (fertilized eggs that have not yet started to divide) are transferred to the fallopian tubes.

Shettles (1909-), knowledge of reproductive physiology was too limited for the IVF procedures to be successful.

It was eventually learned that, after ejaculation (the moment when semen is discharged from the body), sperm undergo changes in their plasma membrane (the thin skin covering every cell). The change that occurs in the sperm's plasma membrane is called capacitation, and it must take place in order to be capable of fertilizing the egg cell. The oocyte (egg) also is not ready for fertilization until just before ovulation occurs.

Armed with this knowledge, researchers successfully fertilized rabbit oocytes in vitro. Min-Chueh Chang (1908-) then went a step further and implanted the IVF-fertilized oocytes into female rabbits. IVF for many other species followed.

The final advance was made by British physicians Robert Edwards and Patrick Steptoe, who began collaborating in 1968. The two doctors developed a method of stimulating ovulation with hormone treatment, then retrieving the nearly mature ova (eggs) and culturing them for the several hours needed for full maturation. Meanwhile, a fresh specimen of male sperm was treated so it underwent capacitation, then it was added to the oocytes in the petri dish, where fertilization took place. The researchers waited until the egg divided into an eight-celled embryo, then transferred it into the woman's uterus where, in successful IVF procedures, it would implant.

Current Success

Although the success rate is considered modest—approximately 20 percent result in a full-term pregnancy—IVF is a widely used infertility treatment. Hundreds of medical centers around the world offer the procedure. Since the mid-1980s, cryopreservation (freezing) of eggs (or embryos) has become a common practice. This involves the preserving of

additional fertilized eggs to be used later, in case the IVF treatment does not produce a pregnancy.

The resulting legal and moral questions of freezing human embryos was dramatized in a 1984 plane crash. A husband and wife who died in the crash left behind cryopreserved embryos in Australia. The sudden deaths raised many questions. What should be done with cyropreserved embryos? Does anyone have the right to dispose of them? How long can they be stored? Who owns them?

Iodine

Iodine is the heaviest member in a family of chemical elements called halogens. The halogen group includes fluorine, chlorine, bromine, astatine, and iodine. Halogens readily combine with other elements to form salts. At room temperature, iodine is a shiny, dark black, nonmetallic, crystalline solid. Good food sources of iodine are fish and shellfish from the sea, as well as other seaweeds. Milk and eggs, vegetables and fruit contain small amounts of iodine.

Properties

Pure iodine is never found in nature—it is always combined with other elements. When iodine is heated it sublimes (passes directly from a solid to a vapor, skipping the liquid state). The iodine vapor is violet colored and has an irritating odor like that of chlorine. The vapor rapidly condenses on a cold surface. Pure iodine is toxic (poisonous).

Iodine is only slightly soluble (capable of being dissolved) in water, but it dissolves easily in a potassium iodide solution. It is also soluble in alcohol, **chloroform,** and other organic substances. Tincture of iodine (iodine dissolved in alcohol) is commonly used to kill germs on cuts and scrapes.

Iodine compounds are found in seawater, soil, and rocks. Iodine is obtained as sodium iodate, an impurity in the sodium nitrate beds in the South American country of Chile (the world's largest source of commercial iodine). Other important sources of iodine are underground pockets of brine (saltwater) found in Michigan, California, and Louisiana.

Most plants and animals require small amounts of iodine for normal growth. In man and other mammals, iodine is concentrated in the thyroid gland (in the neck), where it helps the body make **thyroxine** and other bio-

chemicals that are important in metabolism (the process by which cells provide energy for bodily functions). Without enough iodine, a person's growth may be stunted (halted or slowed), and he may develop a condition called goiter (in which the thyroid gland swells into a large lump).

Today these conditions have been mostly wiped out in the industrialized world by the introduction of table salt containing potassium iodide or sodium iodide.

Courtois Discovers Iodine

Iodine was discovered by French chemist Bernard Courtois (1777-1838) in 1811. Courtois was barely making a living in his family's business of manufacturing saltpeter, which was used to make gunpowder. Saltpeter was made from the ashes of seaweed, which were treated with acid to remove sulfur compounds. One day, Courtois accidentally added too much acid, producing clouds of vapor having an attractive violet color. When the vapor condensed on cold objects, it formed dark, shiny crystals.

Although Courtois investigated the properties of the new substance by combining it with several other elements, he did not have enough time or money to follow through on his discovery. He asked for help from two French chemist friends, Charles Bernard Desormes and Nicholas Clement, who completed the work and made the research public in 1813.

Later that year, **Humphry Davy** and Joseph Gay-Lussac, working independently, showed that iodine was a new element. This research was made public in 1813. Although Davy's and Gay-Lussac's research overlapped, it was Gay-Lussac who gave the new element its name after the Greek word "iodes," meaning "purple." Gay-Lussac went on to study the substance and its compounds, such as hydrogen iodide, in great detail.

In 1831 Courtois received a prize from a French scientific institute for his work. Despite this small measure of fame, Courtois's saltpeter business declined. With the end of the Napoleonic Wars (1804-1815), the demand for gunpowder dropped, and Courtois's factory failed. Although he continued to produce and sell iodine, Courtois had little success, and he died in poverty.

Curing Goiters

In 1814 J. J. Colin made an important discovery in microanalytical chemistry when he showed that iodine reacted with starch to produce a blue color so bright that iodine could be detected in amounts as low as one part in 400,000. In 1819 Jean-Baptiste Dumas proved that sponges used for many years to treat goiter contained iodine. By 1820 iodine had been

discovered in a seaweed called kelp, which had also been used as a goiter treatment. Kelp was one of mankind's earliest sources of iodine. In Japan, kelp is still harvested from the sea and dried under the sun to provide a raw material for iodine production. It is also considered a delicious food by the Japanese, so their diets do not need to be supplemented with iodized salt.

In the mid-1800s, French agricultural chemist Jean Boussingault first suggested that iodine compounds might be able to cure goiter. A young doctor had asked Boussingault to analyze samples of certain salts used by South American Indians to treat goiter. Boussingault found iodine in the salts and suggested the cure, but it was not until 1896 that this treatment was confirmed.

German chemist Eugen Baumann (1846-1896) discovered that the thyroid gland was rich in iodine, which had never been found before in animal tissue. Baumann also determined that the thyroid was the only tissue containing iodine. Just two years later, an Austrian psychiatrist named Julius Wagner von Jaurreg (1857-1940) established that goiter could be prevented by taking iodine tablets regularly. He also proposed that iodized salt be sold in areas where goiter was widespread; Austria and Switzerland later adopted this idea.

The modern use of iodine in the prevention of goiter was a result of studies by D. Marine in the United States. Marine used iodine to prevent goiter in schoolchildren in Akron, Ohio, where the disorder was common. The success of his experiments led to the adoption of this use of iodine in many regions of the world where goiter was a health problem.

Other Iodine Uses

Iodine's most important use is in the health sciences. One of iodine's radioactive isotopes, I-131, is widely used in medical diagnosis as a radioactive tracer. It can also be used to treat thyroid cancer.

In addition to its use as a goiter treatment, iodine serves as an important antiseptic thanks to its germ-killing properties. Tincture of iodine was frequently used to disinfect open wounds. Because of the tincture's irritating sting, however, more complex iodine compounds have been developed for first-aid purposes. Iodine combined with cleaning agents is used in common sanitizers. Iodine is also used to sterilize drinking water.

Iodine has several major industrial uses. Silver iodide is the main light-sensitive substance in photographic film emulsions and photographic papers. Silver iodide is also used by weather scientists for "cloud seeding" in rain-making experiments. Other iodine-containing compounds are used as dyes, in engraving, as an indicator in analytic chemistry, and in special

soaps and lubricants. Commercial bakeries add sodium iodate to certain kinds of flour to improve the quality of the bread. Some inorganic iodides are used in producing high-purity titanium and silicon metals.

Iron lung and other respirators

The iron lung was invented in 1929 by Philip Drinker (1893-1977), a professor at the School of Public Health at Harvard University. The device performs the function of the muscles that control breathing. It was one of the first of several inventions designed to keep people alive who are unable to breathe unassisted.

Pulmonators

During the 1920s people who could not breathe on their own were aided by a pulmotor. This was a machine similar to fireplace bellows. It inflated and deflated the lungs by forcing air in and then sucking it back out again. The process worked, but some patients experienced chest pain. Many people suffering from polio or infantile paralysis required such a device. The polio virus can damage the nervous system causing paralysis of the diaphragm. Without the movement of the diaphragm, polio-sufferers often died by suffocation.

Drinker's Research

Drinker got his idea from a Swedish physician named Thunberg, who had been experimenting with a vacuum device to help patients breathe. Drinker enlisted the help of his brother, Cecil, and Louis Shaw (1886-1940) to build a prototype (model) based on Thunberg's principles. He tested the first machine on cats and then designed one large enough for a human patient.

The patient's head was positioned outside the box while the rest of the body was enclosed in the airtight metal box. A pump connected to the box varied the air pressure inside the chamber. When the air pressure inside the box decreased, the weight of the atmosphere outside the box forced air through the nose and mouth into the lungs. When the air pressure in the box increased, the air was forced out of the lungs.

Drinker's invention was first known as the "Drinker tank respirator" but was soon given the nickname of "iron lung." Drinker and Louis Shaw received numerous awards for their invention. The iron lung allowed

Iron lung and other respirators

many polio patients to live longer lives. It was used from 1928 well into the 1950s.

Ventilators

Since Drinker's time, a sophisticated class of breathing machines called ventilators, or respirators, has been developed. A modern ventilator consists of an electrical pump connected to an air supply, a humidifier that adds water to the air, and a tube inserted into the patient's nose or mouth. Ventilators use positive air pressure from the pump to force air into the lungs. The ventilator pumps air into the lungs for a preset time or volume and then stops. The patient then exhales the air naturally.

To adjust the ventilator properly, a blood sample from the patient is analyzed. This determines the metabolic rate and the optimal oxygen-carbon dioxide ratio. Then the volume of air needed and the number of times per minute the person should breathe to maintain the desired metabolic rate

Patients being treated in iron lungs. Today, the iron lung of the 1950s is making a comeback. Because it uses non-invasive technology and negative air pressure, it does not cause infections or scarring of the trachea.

is calculated. When properly connected, positive air pressure brings just the right volume of air into the lungs. Then the lungs passively deflate when the ventilator shops filling the lungs. Today's sophisticated hospital respiratory care units may utilize up to 15 different kinds of respirators.

Ventilators aid patients who have paralyzed muscles, suffer from degenerative muscle disease, or have burns in the nose and throat. When patients are to be hooked up to a ventilator for months at a time a breathing tube is surgically inserted directly into the windpipe. Miniature ventilators are used to help premature babies breathe. They are also used to help patients who have undergone surgery and need temporary help from a machine.

In some places, the iron lung of the 1950s is making a comeback. Because it uses non-invasive technology and negative air pressure (a vacuum), it does not cause infections or scarring of the trachea. It can be used at home to help a patient rest the respiratory muscles during the day or night.

Mini-iron lungs are now used for some patients. Nicknamed "turtles" because of their green color and shell-like shape, these miniature devices can be strapped onto a patient's chest.

Jenner, Edward

Edward Jenner (1749-1823) was a pioneer in the study of viruses and immunization against diseases. His work has been built upon by many successors who have discovered new vaccinations to reduce suffering and death, particularly for children.

Jenner was born in Berkeley, England, the youngest of six children born to Stephen Jenner, a clergyman of the Church of England. Jenner's father died when he was only five years old, and he was raised by his older brother, who was also a clergyman.

In agreement with the practice at the time, eight-year-old Jenner was forced to fast (not eat for long periods), had blood drawn from him in a practice called "bleeding," and was injected with smallpox (in the hope that the injection would prevent the disease).

When Jenner was thirteen years old, he was apprenticed (became an assistant in training) to a surgeon. Then in 1770, he moved to London, England, to work with John Hunter (1728-1798), a famous Scottish anatomist and surgeon who encouraged Jenner to be curious and experimental in his approach to medicine. Jenner returned to Berkeley in 1773, and set up practice as a country doctor. His curiosity led him to conduct his own research to help his rural patients.

Edward Jenner. Thanks to Jenner's curiosity and perseverence, smallpox has been eradicated worldwide.

Smallpox

Up until Jenner's time, smallpox was a common and often fatal disease worldwide. It caused high fevers and ugly pockmark scars, like those of chicken pox, only these scars could disfigure a person for life.

Many centuries before Jenner's time, the Chinese had begun the practice of blowing flakes from smallpox scabs up the nostrils of healthy persons to produce immunity to the disease. By the seventeenth century, the Turks and Greeks had discovered that, when injected into the skin of healthy individuals, the serum from the smallpox blister produced a mild case of the disease and subsequent immunity.

The practice of inoculation reached England by the eighteenth century. It was quite risky, since those who were inoculated frequently suffered a severe or fatal case of smallpox. Despite the risk, people willingly agreed to inoculation because of the widespread incidence of smallpox and the fear of suffering terrible disfigurement.

Jenner's Experiments

As a young physician, Jenner noticed that dairy workers who had been exposed to cowpox, a disease like mild smallpox, seemed immune to the more severe infection. Jenner continually put forth his theory that cowpox could be used to prevent smallpox, but his fellow physicians shunned his ideas. They maintained that they had seen smallpox victims who claimed to have had earlier cases of cowpox, so that cowpox must not give immunity. It became Jenner's task to transform a country superstition into an accepted medical practice.

After many years of observing cases of cowpox, Jenner took a step that could have branded him a criminal as easily as a hero. On May 14, 1796, he removed the fluid of a cowpox blister from dairymaid Sarah Nelmes, and inoculated James Phipps, an eight-year-old boy who soon came down with cowpox. Six weeks later, he inoculated the boy with smallpox. The boy remained healthy, and Jenner had proved his theory. Jenner called his method "vaccination," using the Latin word "vaccinia," meaning "cowpox."

The publication of Jenner's *An Inquiry into the Causes and Effects of the Variolae Vaccinae* set off an enthusiastic demand for vaccination throughout Europe. Within 18 months, the number of deaths from smallpox had dropped by two-thirds in England. By 1800, 100,000 people had been vaccinated worldwide. As the demand for the vaccine rapidly increased, Jenner discovered that he could take lymph from a smallpox

pustule and dry it in a glass tube for use up to three months later. The vaccine could then be transported.

Jenner became famous throughout Europe and the United States. Across the Atlantic Ocean, Thomas Jefferson received the vaccine from Jenner and proceeded to vaccinate his family and neighbors at Monticello. In his native England, however, Jenner's medical colleagues refused to allow him entry into the College of Physicians in London, insisting that he first pass a test on the theories of the ancient Greek physicians, **Hippocrates** (460-377 B.C) and **Galen** (A.D. 130-200). Jenner refused to bow to their demands, saying his accomplishments in conquering smallpox should have qualified him for election. He was never elected to the college.

Jenner continued to live in his country home and practice medicine in the years after his discovery. He also pursued his interest in birds and wrote papers on their behavior until his death in 1823. His work had far-reaching effects, inspiring **Louis Pasteur** (1822-1895) in his research on the causes of disease, thus leading to vaccines for other serious illnesses. And today, thanks to Jenner's curiosity and perseverence, smallpox has been largely eradicated (erased).

Kidney transplant

Replacing a kidney is a difficult process because the kidney acts as a filter for the body. Its functions are to excrete (get rid of) urine which contains the end products of metabolism and help regulate the water, electrolyte level, and the acid base content of blood. As a complex filter, it allows the body to maintain adequate levels of glucose (a chrystal-like sugar compound), magnesium, and other chemicals needed for regular bodily functions.

Transplant Difficulties

Although the kidneys have a relatively simple blood-supply system, they initially proved difficult to transplant. As early as 1933, attempts were made to **transplant** a kidney. Problems with the body's rejection of the new organ were the principal reasons for failure. It wasn't until 1954 that the first successful transplant was made. One of the principal reasons for the success of the surgery was that the kidney donor was an identical twin of the patient. Because the donor and the patient were so closely related, their body tissues were excellent matches.

Once the procedure gained this limited success, the next thrust of research was to find a means for reducing the rejection of the organ. In 1962 the matching of body tissues between the recipient and prospective organ donors increased the success rate for kidney transplants. Then, in that same year Imuran (azathioprine) was used as an immunosuppressant and the success rate increased again.

Cyclosporine

About ten years later in 1972, **cyclosporin** ushered in an era of widespread organ transplants. Leading the way in kidney transplantation was British surgeon Roy Calne. By 1963 Calne had published a standard text on kidney transplantation. Working closely with his associate David White, Calne experimented with cyclosporin. This drug was supplied by Swiss scientist Jean-Francois Borel. After extensive tests and trials, cyclosporin became the standard drug to be used for transplants of all types. Combining this drug with **steroids** further increased the success rate for these types of surgeries.

[*See also* **Steroids**]

Kitasato, Shibasaburo

Bacteriologist Shibasaburo Kitasato (1852-1931) made several important contributions to the understanding of human disease and how the body fights off infection. He also discovered the bacterium that causes bubonic plague.

Born in Kumamoto, Japan, Kitasato completed his medical studies at the University of Tokyo in 1883. Shortly after, he traveled to Berlin to work in the laboratory of **Heinrich Robert Koch** (1843-1910). While at the lab, Kitasato discovered a way of growing a pure culture of tetanus bacillus. In the following year, Kitasato and German microbiologist **Emil von Behring** (1854-1917) reported on the discovery of tetanus and diphtheria antitoxin (a substance that neutralizes poisons).

Shibasaburo Kitasato.

The researchers found that animals injected with the microbes that cause tetanus or diphtheria produced substances in their blood, that neutralized the toxins produced by the microbes. Furthermore, these antitoxins could be injected into healthy animals, providing them with immunity to the microbes. This was a major finding in explaining the workings of the immune system and in the development of vaccines for diseases.

In 1892 Kitasato returned to Tokyo and started his own laboratory. Seven years later, the

Japanese government took over the laboratory, but kept him as director. When the laboratory was consolidated with the University of Tokyo, however, Kitasato resigned and founded the Kitasato Institute.

Kitasato Fights Plague

During an outbreak of the bubonic plague (a contagious disease spread by the fleas of contaminated rats) in Hong Kong in 1894, Kitasato was sent by the Japanese government to research the disease. He was able to isolate the bacterium that caused it. Four years later, Kitasato and his student Kigoshi Shiga were able to isolate and describe the organism that caused dysentery (an infection of the lower intestinal tract producing pain, fever, and severe diarrhea) as well.

Kitasato was named the first president of the Japanese Medical Association in 1923 and was made a baron by the Emperor in 1924. He died in Japan in 1931.

Koch, Heinrich Hermann Robert

Heinrich Hermann Robert Koch's (1843-1910) research helped prove French researcher **Louis Pasteur**'s (1822-1895) theory that germs, or small microorganisms, caused diseases. Koch also worked diligently to find the causes of diseases such as cholera (a severe intestinal disease) and tuberculosis (an infectious disease of the lungs).

Early Life

One of thirteen children born to a mining engineer and his wife, Koch spent his youth in the Harz Mountains in Clausthal, Germany. During Koch's adolescent years, his father insisted he learn the shoemaker's trade. When money became available for an academic career, however, Koch entered the University of Göttingen as a student of medicine and natural science at the age of 19. He graduated in 1866.

After service as a surgeon in the Franco-Prussian War (1870-1871), Koch started a practice as a country doctor in Wollstein, what is now Wolsztyn, Poland. At this time he also began his microscopic studies of bacteria. One of Koch's most important developments was a technique to use gelatin on glass slides to produce a transparent background for examining microorganisms. Koch's techniques are still used in the study of diseases.

Koch Studies Anthrax

One of Koch's early projects was to discover the cause of anthrax, a deadly disease of cattle and sheep. For years, farmers had been confused about outbreaks of anthrax in fields where infected cattle had been removed years earlier. After isolating strains of the anthrax bacillus, Koch showed that, under certain conditions, the bacilli formed spores (a tiny reproductive body) that could remain dormant Inactive) for several years. These spores remained in infected fields and could develop into the disease-causing anthrax bacillus if conditions were right.

By the late nineteenth century, researchers such as Pasteur had put forth the germ theory of disease, but no one had been able to prove that a single identifiable microorganism was responsible for a given disease. Koch's publication of his work with the anthrax bacillus helped prove that Pasteur was right.

Koch and Cholera

In 1883 Koch turned his attention to cholera, a very infectious disease that causes often fatal cases of diarrhea. In intense competition with Pasteur (who had taken a team to Egypt), Koch also took a group of German scientists to Egypt in an attempt to win the race to isolate the causative (responsible) agent. But the epidemic in Egypt ended before Koch's research was completed. He subsequently went to India, where he was able to isolate the comma-shaped bacillus responsible for cholera, Vibrio cholerae, from samples of drinking water, food, and clothing.

The Four Postulates

Koch became famous for his discoveries in the field of bacteriology. In 1885 he was named director of the new Institute of Hygiene in Berlin, Germany. Five years later, Koch published the "Four Postulates" ("four rules") on which modern bacteriological studies have been built. The postulates are:

- The organism must be present in every case of the disease.
- The organism must be cultivated in a pure culture.
- The organism must produce the disease in a susceptible animal upon inoculation.
- The organism must produce the same disease when healthy animals are inoculated.

Tuberculosis Studies Causes Controversy

Koch also contributed to the study of tuberculosis, a disease which attacks the lungs and slowly destroys them. In 1882 he was able to isolate Mycobacterium tuberculosis, the tiny bacillus that causes tuberculosis. It was Koch's search for a cure for tuberculosis, however, that would cause him temporary shame in the eyes of his fellow researchers. He thought he had found the cure, and in 1890, under pressure from the German government, he announced that he had "at last hit upon a substance that has the power of preventing the growth of the tubercle bacillus not only in the test-tube, but in the body of an animal."

Thousands of tubercular patients rushed to Berlin for tuberculin treatment. Those inoculated (injected with the vaccine) eventually died of miliary tuberculosis, considered the worst form of the disease. Koch, who had always conducted his research in secrecy, was forced to reveal the method he used to obtained tuberculin. In his search for a cure, he had cultured tubercle bacilli, heat-killed them, and filtered off the liquid. He had hoped to develop an effective vaccine from this method. But rather than discovering the cure for tuberculosis, Koch actually had discovered the substance that is now used to diagnosis the disease.

Despite the disappointment with his tuberculosis error, Koch received the 1905 Nobel Prize for medicine for his work with tuberculosis. He died in 1910, before he or any of his German colleagues could find a cure for tuberculosis. But his achievement in proving the germ theory of disease was critical to the development of vaccines and cures for many diseases.

[*See also* **Inoculation**]

Laparoscopic surgery

Laparoscopic surgery has become a common method for treating a variety of abdominal medical problems. To insert the laparoscopic version of the endoscope (an **endoscope** is an optical instrument that allows doctors to see inside the human body; also referred to as a fiberscope), doctors make tiny incisions instead of the usual large cuts across the surgical area. After the incisions are made, carbon dioxide is blown into the abdomen through the navel to make a space for small video cameras and scalpels to do the actual surgery. This technique dramatically reduces the amount of trauma to the patient's body tissues and shortens surgery and recovery times.

Early Laparoscopic Techniques

The laparoscopic technique was introduced in the 1960s by Raoul Palmer of the Broca Hospital in Paris, France, to help diagnose gynecological (sexual organ) problems in women. At first, Palmer had to use a bicycle pump to get air into the abdomen. He also had to use a regular laboratory scope rather than a video camera to see into the body.

Tiny Blades Make the Difference

It was not until 1986 that laparoscopy was used for actual surgery rather than just diagnosis. By this time, tiny remote-control scalpels had been developed that allowed doctors to use Palmer's techniques for surgical procedures. These small scalpels could be attached to the tip of the endoscope to manipulate tissue and draw samples for diagnosis and treatment.

The main disadvantages of such procedures are the cost, which is greater than for conventional surgery, and the temptation to perform

The Flexible Endoscope

An endoscope is a narrow, flexible tube containing several bundles of glass fibers that are covered with a reflective coating. An intense light source is used to transmit light along one bundle of fibers to the target, or surgical, area. Different types of endoscopes are specially designed for use in specific parts of the body. The angioscope passes through the arteries that carry blood to the heart; the **arthroscope** is used to explore the interior area of joints; the bronchoscope is used with a special dye and florescent light to detect lung growths; and the laparoscope is used for the diagnosis and treatment of abdominal conditions.

surgery when other, more conservative, therapies might do just as well. There are also the risks associated of any kind of surgery, such as excessive bleeding, or patient reaction to **anesthesia.**

Although laparoscopy was received with skepticism by surgeons at first, it is now widely used in gynecology. It is also being adapted for other types of surgery, particularly for the cardiovascular (heart and blood vessel) system, and more recently, to treat certain cancers. In the future, laparoscopic techniques may be used so that a surgeon can perform an operation by remote control on a patient in another city or even country.

Larrey, Dominique-Jean

Dominique-Jean Larrey (1766-1842) was instrumental in improving conditions for wounded soldiers during wartime. He perfected better **amputation** techniques and invented the **ambulance** as a way to reduce casualties by swiftly removing wounded men from the battlefield.

Larrey was born in France. After learning the medical practices of the time, he went to work for Napoléon Bonaparte (French emperor from 1804-1814) during the emperor's various campaigns from 1792 through 1814. It was during these campaigns that Larrey developed numerous improvements in the handling of wounded soldiers.

Larrey set up the first field hospitals by placing medical tents close to battle instead of miles away in centralized areas. In 1792 he started a horse-drawn carriage ambulance service to and from fighting areas. By

1794 Larrey had added stretchers to his ambulance design. In the Egyptian campaign of 1799, he used camels to power his ambulances.

With fellow surgeon Pierre Percy (1754-1825), Larrey formed a unit of "ambulance soldiers," including stretcher-bearers and trained doctors. Larrey's ambulances and medical units both impressed Napoléon's troops and boosted their morale.

In addition to creating the ambulance prototype, or model, Larrey became an expert in field amputations, at one point performing 200 amputations in 24 hours. As he worked with the open wounds of battle, Larrey also discovered that a wound would heal better, with less chance of infection, if it were cleaned and allowed to remain open for several days before being sutured (stitched up).

Laser surgery

The term "laser" is an acronym for **L**ight **A**mplification by the **S**timulated **E**mission of **R**adiation. The elements necessary for the invention of the first laser have been around for quite some time. Theories of coherence (pertaining to waves with a continuous relationship) and stimulated emission (active discharge) were discussed in detail by Albert Einstein (1879-1955) in 1917, but were presented only as hypotheses (theories). In his writings, Einstein never described a device that could achieve stimulated emission. This was the case until 1954, when American physicist Charles Townes (1915-; 1964 Nobel Prize winner) accomplished stimulated emission using microwaves.

Laser Development

With proof that stimulated emission of light was possible, scientists around the world raced to create a working laser. In 1958 Townes and Arthur Schawlow (1921-) delivered a paper that explored the requirements for a laser radiator. At the same time, American physicist Gordon Gould (1920-) designed a working laser model and coined the familiar term. Due to a misunderstanding at the patent office, however, Gould did not apply for a patent (registration) of his design. Townes and Schawlow eventually received the patent, but it was Theodore Harold Maiman (1927-) who received credit for the laser's invention.

In 1960 Maiman constructed the first working laser in the United States. While F. A. Butayeva and V.A. Fabrikant of the Soviet Union

worked on the process at the same time, they did not publish their findings and received almost no credit for their pioneering efforts.

Lasers went to work almost as soon as their discovery was announced. Unhampered by distances, early laser beams were directed at the moon and reached within two miles of their planned destination. Lasers, when focused through a lens, were able to cut diamonds with absolute precision.

How Lasers Work

To understand how a laser works, it is important to know how all light functions. Normal light, like sunlight, is emitted (sent out) from its source in all directions and is called spontaneous emission. Laser light is generated within a medium (a type of device or environment). The atoms within the medium are excited but still require some form of stimulus (motivation) to emit light. In Maiman's laser, a flash tube was wrapped around a

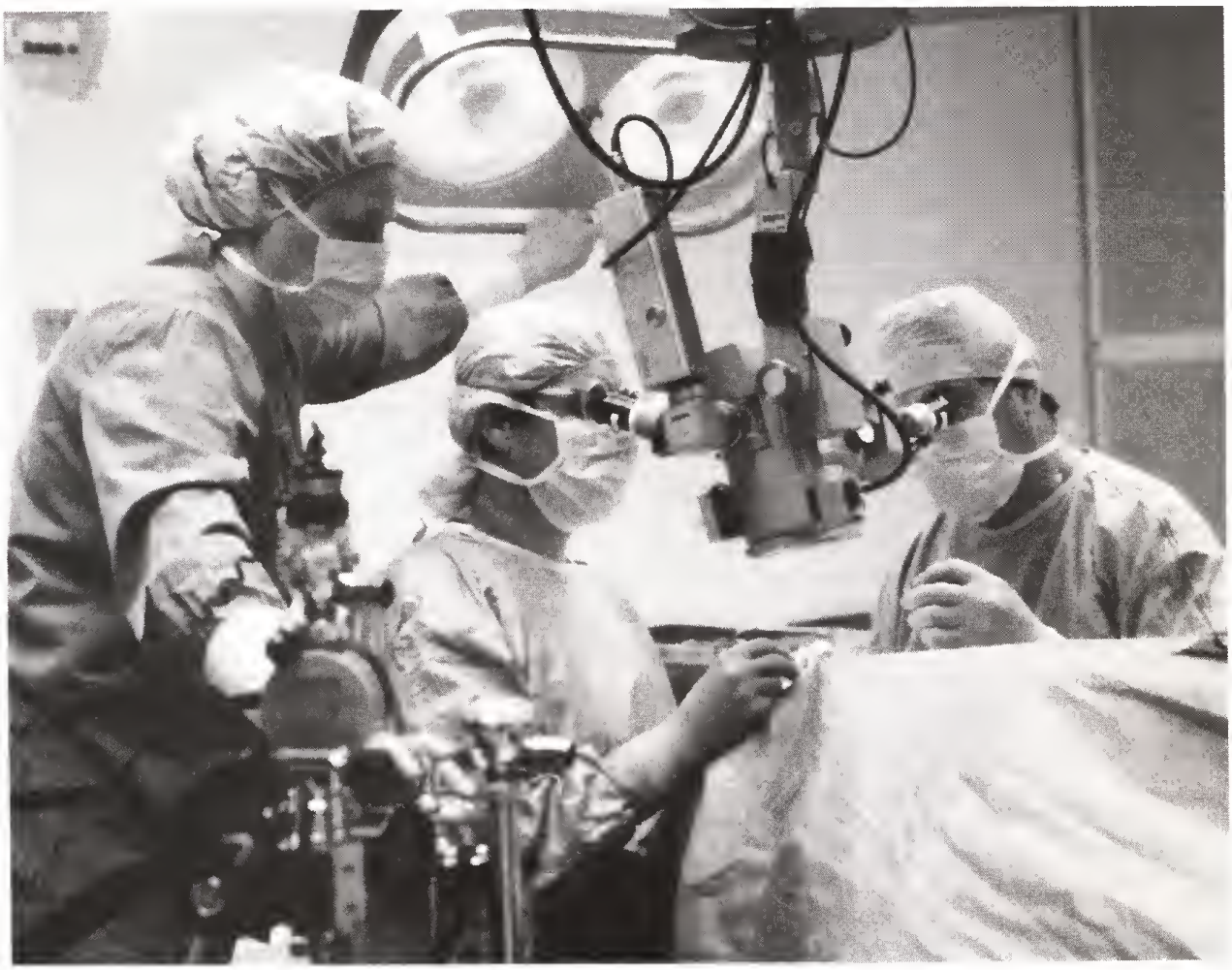
A modern industrial laser. Lasers are also often used for surgery where anesthesia is not required.

ruby rod. The flash started a chain reaction that ended with a beam of red light escaping from the rod. This sort of chain reaction is called stimulated emission and is the basis for laser technology.

Lasers are used industrially in a wide variety of products. Laser-cut wood products exhibit great precision. Compact discs on which music and electronic data are stored have been made possible by the laser. These discs are capable of saving their information without distortion or fading for long periods of time.

Medical Use

By 1962 efforts at using the laser for medical purposes were underway. The ruby crystals through which early lasers were transmitted did not lend themselves to medical use. It wasn't until argon (a colorless, oderless intert gas) gas was used in place of the ruby that the correct color and intensity of the laser beam was able to be harnessed for surgery.



Laser eye surgery. Lasers are also used to remove birthmarks and wrinkles, reopen blocked arteries, and seal blood vessels to prevent bleeding.

Lasers are used regularly for short surgical procedures where no **anesthetics** are required and for other surgeries where extreme precision is needed. Examples of anesthetic-free surgeries are those of the eye where detached retinas are repaired and cataracts are removed. Lasers are also used to remove birthmarks from the skin, remove wrinkles, reopen blocked arteries, and seal blood vessels to prevent bleeding.

Leeuwenhoek, Antoni van

Antoni van Leeuwenhoek (1632-1723) is best remembered as the first person to study bacteria and one-celled animals now known as protozoa. Unlike his contemporaries, Leeuwenhoek did not use the more advanced **compound microscope.** Instead, he tried to manufacture magnifying lenses of great power and clarity that would allow him to study microcoorganisms in far greater detail than any other scientist of his time.

Early Career

Although Leeuwenhoek's family was fairly well off, he received little formal education. After completing grammar school in Delft, Netherlands, he moved to Amsterdam to work as a draper's apprentice (a draper was a person who made and sold clothing). In 1654 he returned to Delft to establish his own shop and worked as a draper for the rest of his life. His medical achievements in lens grinding were actually a hobby rather than his main work. Lenses were an important tool in Leeuwenhoek's profession, since cloth merchants often used small lenses to inspect their products. His hobby soon turned to obsession, however, as he searched for more and more powerful lenses.

In 1671 Leeuwenhoek made his first simple microscope. It had a tiny lens that he had ground by hand from a globule (small ball) of glass and had placed in a brass holder. To this he had attached a series of pins designed to hold the specimen. It was the first of nearly six hundred lenses ranging from 50 to 500 times magnifications that he would grind during his lifetime.

Through his microscope Leeuwenhoek examined such substances as skin, hair, and his own blood. He studied the structure of ivory as well as the physical composition of the flea, discovering that fleas, too, had even smaller parasites on them.

Leeuwenhoek began writing to the British Royal Society in 1673 about his discoveries. At first, the Society gave his letters little notice,

thinking that such magnification from a single lens microscope could only be a hoax (fake). The best microscopes had more than one lens to provide better clarity. In 1676, when he sent the Society the news that he had discovered tiny one-celled animals in rainwater, scientists became interested in his work. Following Leeuwenhoek's instructions, they built microscopes of comparable magnitude and confirmed his findings. In 1680 the Society unanimously elected Leeuwenhoek as a member.

Further Research

Until this time, Leeuwenhoek had been operating without any information on what other microscope developers were doing. He read only in Dutch and was unable to learn from the published works of Hooke and Malpighi, the other great microscopists of the time. As a member of the Royal Society, however, he was finally able to correspond with other scientists. In fact, the news of his discoveries spread worldwide, and he was often visited by royalty from England, Prussia, and Russia. The traffic through his laboratory was so persistent that he eventually allowed visitors by appointment only. Near the end of his life he had reached legendary status, and was often referred to by the local townsfolk as a magician.

Amid all the attention, Leeuwenhoek remained focused upon his scientific research. Specifically, he was interested in disproving the common belief in spontaneous generation, a theory proposing that certain inanimate (non-living) objects could generate life. For example, it was believed that mold and maggots were created spontaneously from decaying food. He succeeded in disproving spontaneous generation in 1683 when he discovered bacteria cells. These tiny organisms were nearly beyond the resolving power of even Leeuwenhoek's remarkable equipment and would not be seen again for more than a century.

Leeuwenhoek created and improved upon new lenses for most of his long life. For the forty-three years that he was a member of the Royal Society, he wrote nearly 200 letters that described his progress. However, he never wrote about the method he used to light up his specimens for viewing, and the nature of that lighting technique is still a mystery. Upon his death, Leeuwenhoek willed twenty-six of his microscopes—a few of which survive in museums—to the British Royal Society.

[*See also* **Microscope, compound**]

Lister, Joseph

Joseph Lister (1827-1912) developed **antiseptic** surgery, saving innumerable patients from the dreadful pain and death of post-surgical infection by ensuring that surgical wounds were sterile. Lister was born in Upton, Essex, the son of a London wine merchant. His father invented the achromatic lens, which led to the development of the modern microscope. The senior Lister naturally encouraged his son's interest in microbiology. After receiving his medical degree from University College Hospital in London in 1852, Lister practiced and taught surgery, first in Edinburgh, Scotland, and from 1860, in Glasgow, Scotland.

As a surgeon, Lister became increasingly disturbed by the high rate of often fatal infections that developed in his patients after surgery.

As a surgeon, Lister became increasingly disturbed by the high rate of often fatal infections that developed in his patients after surgery. A professor of chemistry, Thomas Anderson (1819-1874), drew Lister's attention to the ideas of French chemist and microbiologist **Louis Pasteur.** After reading some of Pasteur's findings, Lister concluded that the germs described by Pasteur as being carried in the air caused wound infections. As a result, Lister developed a method to destroy these organisms using carbolic acid as an antiseptic.

Lister's Antiseptics

Lister first used his new antiseptic surgical technique in March 1865. Although this and many subsequent operations proved the effectiveness of Lister's method to prevent infection, Lister's ideas were opposed by many of his fellow physicians, who thought the antiseptic procedures ridiculously complicated and unnecessary.

In 1877 Lister became a professor at London's King's College Hospital, where he continued to promote his antiseptic methods. He also poineered the use of absorbable sutures (stitches) and the introduction of wound drainage. Eventually the medical community was won over by his success. By the late 1870s and 1880s, Lister had gained many honors (including royal titles) and was a greatly respected figure. He died in 1912.

Lithium

Lithium is an alkali metal. It is silvery white in color. When burned, it gives off a crimson glow. Lithium occurs in nature only in compound form. The story of lithium's discovery began in 1800 with a report by a Brazilian scientist named José Bonifacio de Andrada e Silvio. He discovered two met-

als while traveling in Sweden and called them "spodumene" and "petalite." These two metals were rediscovered by a Swedish chemist, E. T. Svenenstjerna. Investigation of the metals was puzzling, because anywhere from one to ten percent of the components was unaccounted for during chemical analysis.

Arfvedson's Studies Lead to Discovery

The explanation for this problem was provided by Johan August Arfvedson, a young man working in the laboratory of Jöns Berzelius. The components Arfvedson identified in the mineral added up to 95 or 105 percent, but never 100 percent. He concluded that these results could be explained only by the presence of a new element in the mineral. He proposed the name "lithium" for the new element, which comes from the Greek word "lithos," or "stone."

Arfvedson was never able to isolate the pure metal itself. That was accomplished by W. T. Brande (1788-1866) and **Humphry Davy** (1778-1829) working independently in 1818. The men obtained the metal through electrolysis of lithium oxide. By 1855, Bunsen and Matthiessen had discovered a way to produce the metal in large quantities and could manufacture a few grams of it in a matter of minutes.

Researchers soon found lithium in both plants and animals, although only in small amounts. In 1860, Gustav Kirchhoff and Bunsen found lithium in the ash of grapes, tobacco, kelp, and in milk. Later, researchers also found the element in human urine, bones, and teeth.

Medical Uses

A number of lithium compounds have important pharmacological effects. Lithium carbonate is the most commonly used of the compounds. In the early nineteenth century, these compounds were used to treat gout (an illness characterized by a painful swelling of the joints), and lithium bromide was used to induce sleep.

In 1949, J. F. J. Cade of Australia was looking for toxic (poisonous) nitrogenous substances in the urine of mental patients by testing guinea pigs. He administered lithium salts to the animals in an attempt to increase the solubility of urates so that they would be secreted more readily in the urine. Lithium carbonate, one of the salts, made the animals sleepy. He then gave lithium carbonate to severely agitated or manic patients. He reported that this treatment seemed to have a dramatic effect on mania.

Lithium carbonate was not accepted for use in the United States until 1970, however, owing to fears about its safety. These fears existed because

doctors in the 1940s had used lithium chloride as a salt substitute in heart patients and others who were chronically ill. This was ill-advised and led to severe toxicities (poisonous reactions) and death.

Today lithium carbonate successfully controls the wild mood swings from depression to elation observed in manic-depressive illness (also known as bipolar disorder). It produces the most dramatic therapeutic improvement of any drug used in psychiatry.

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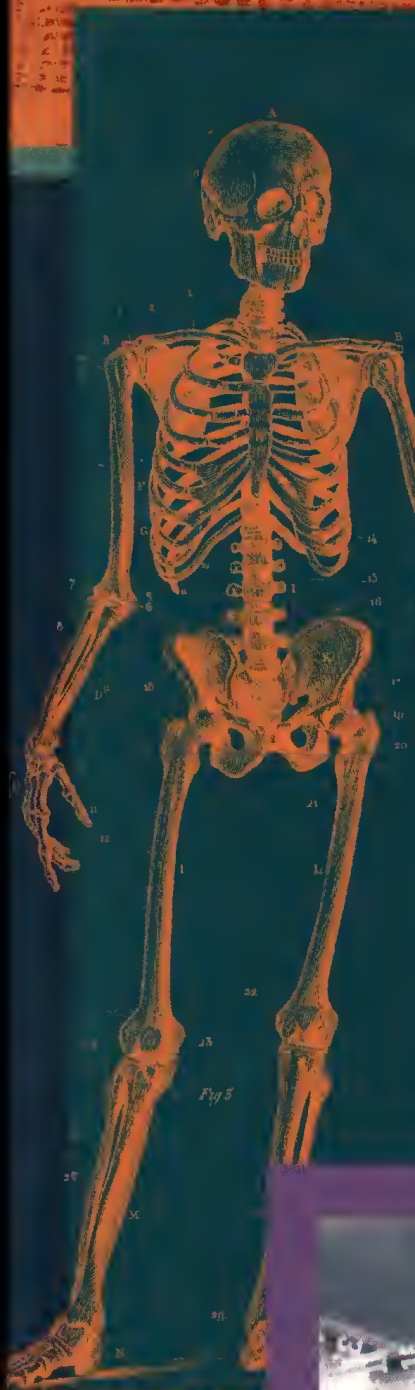

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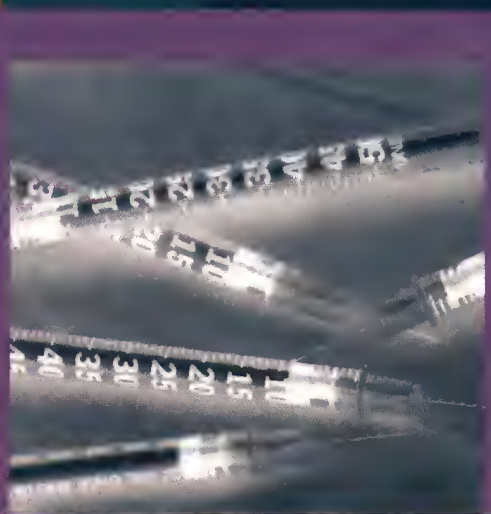

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